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# Nedocromil sodium as single dose prophylactic treatment of exercise-induced bronchoconstriction in asthma: a meta-analysis

by

Carol Helen Spooner

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science

in

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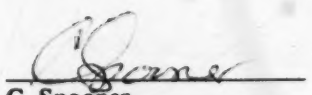

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22 April 1998

## Abstract

A meta-analysis of 20 randomised, controlled trials to assess the effect of nedocromil sodium (NCS) in preventing exercise-induced bronchoconstriction (EIB).

Search strategy: Cochrane Airways Review Group RCT register, Current Contents, Cochrane Controlled Trials Register, bibliographies, the drug manufacturer and authors. No language restrictions.

Selection Criteria: Confirmed EIB, rigorous exercise challenge, measures of forced expiratory volume in one second (FEV1) or peak expiratory flow rate (PEFR).

Main outcomes: maximum percent fall FEV1/PEFR, effect over 30 minutes post-exercise, adverse effects. Results pooled and reported as the weighted mean difference (WMD) using the random effects model.

Main results: NCS had a significant inhibiting effect on EIB. WMD (maximum % fall FEV1) 15.6% [95% CI: 13.1, 18.1%], a protective effect of 51% [95% CI: 46, 55%] over placebo. Time to recovery less than 10 minutes. Significant differences in subgroup analyses based on severity. WMD in mild EIB 12.8% [95% CI: 10.0, 15.7%] compared to 21.4% [95% CI: 17.2, 25.5%] in more severe EIB. No significant adverse effects reported.

Conclusions: The prophylactic use of NCS was effective in inhibiting EIB.

## Dedication

*This thesis is dedicated to my husband, Rick, whose support, encouragement, assistance, and endurance have meant more to me than words can say. Your love truly is patient, kind, trusting, hopeful and giving, your love has never failed and always provided the protection and motivation I needed. Thank you.*

*I want to give thanks to our three children, Ben, Jillian and Trudy, who were often pressed into service on the domestic and academic fronts. Each of you is the joy of our lives and a special gift to treasure always.*

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## Abbreviations

| | |
|---|---|
| $\chi^2$ | chi-square statistic |
| $\beta_2$ agonist | beta 2 agonist |
| 95% CI | 95% confidence limits |
| ARG | Airways Review Group |
| ATS | American Thoracic Society |
| BHR | bronchial hyperreactivity |
| CC | Cochrane Collaboration |
| CCG | Canadian Consensus Guidelines |
| CCTR | Cochrane Controlled Trials Register |
| CDSR | Cochrane Database of Systematic Reviews |
| $Cl^-$ | chloride ion |
| CRG | Cochrane Review Group |
| df | degrees of freedom |
| EIB | exercise-induced bronchoconstriction |
| $FEF_{25-75}$ | forced expiratory flow at 25 - 75% of vital capacity |
| FEV1 | forced expiratory flow in one second |
| FVC | forced vital capacity |
| max % fall | maximum percent fall |
| MDI | metered dose inhaler |
| MetaView | program within RevMan to view graphs |
| N | number of studies |
| n | sample size |
| NCS | nedocromil sodium |
| NCS | Nedocromil sodium |
| NSAID | Non-steroidal anti inflammatory |
| PEFR | peak expiratory flow rate |
| PFT | Pulmonary function test |
| RCT | Randomised, controlled trial |
| RevMan | Review Manager 3.0.1 software program |
| SCG | sodium cromoglycate |
| SD or sd | standard deviation |
| SOB | short of breath |
| var | variance |
| WMD | weighted mean difference |

# Chapter one

## Section 1: Overview of exercise-induced bronchoconstriction

### 1.1.1 Introduction

> *Like beech-nuts seeded in the clay of some Chiltern ridge waiting for the sun to warm them, the mast cells play a waiting game. They lurk for years, decades even, in the walls of the bronchial tubes, until mobilised by the approach of an eligible allergen... and whoosh (they) discharge their malign granules in one vengeful, triumphant burst. The tube-walls swell, the passages narrow and the attack begins. In such frightful terrain, almost anything could trigger off hostilities. In my case, it happened to be the sports day, and especially the father's race, that did it.*
>
> Ferdinand Mount *Of Love and Asthma*

In this comic work of English fiction, Mr. Mount's character was suffering from exercise-induced asthma, a condition first recorded around 150 AD by Aretaeus, of Cappadocia (cited in Virant, 1997). This condition goes by several labels in the literature, among the more common are: exercise-induced asthma, exercise-induced bronchospasm or bronchoconstriction, exercise-induced airway narrowing, and exertional asthma. It affects a broad segment of the population, particularly those who have asthma, or bronchial hyperreactivity (BHR), and people who are atopic or have allergic rhinitis (Rupp, 1996). The underlying pathology is believed to involve airways that are hyperreactive, either to irritants or immunologic stimuli and that trigger bronchoconstriction, thus, the term 'exercise-induced bronchoconstriction' (EIB) is a more accurate term to depict the condition and was adopted for this thesis.

### 1.1.2 Definition of Exercise-induced bronchoconstriction

EIB is defined as a transient increase in airway resistance due to bronchoconstriction brought on by six to eight minutes of strenuous exercise (Anderson, 1985b). Objective measures of the changes in airflow, which quantify the degree of constriction, are obtained from two measures of pulmonary function: the forced expiratory volume at one second (FEV1), or the peak expiratory flow rate (PEFR). A

post-exercise reduction of 10% or more compared with pre-exercise baselines in either measure is considered diagnostic of EIB (Anderson, 1975).

EIB is associated with hyperinflation of the lung and gas trapping in the alveoli leading to arterial hypoxemia (Anderson, 1981). Common symptoms experienced during an EIB episode include cough, wheeze, shortness of breath, chest tightness, chest pain, or an 'itching or scratching sensation' in the chest. Less common are stomach pain and nausea. EIB is also associated with lack of endurance during exercise and prolonged recovery time following exercise (Virant, 1992). The hallmark of EIB is that the constriction generally peaks rapidly, between three and fifteen minutes after exercise stops, followed by a slower spontaneous return to pre-exercise flow patterns within 60 minutes (ibid). EIB is, in appearance, an asthma attack that is indistinguishable from attacks provoked by other stimuli, except that, in general, episodes are short lived, remit spontaneously, and do not result in prolonged deterioration in lung function (McFadden, 1994; Anderson, 1995). A small subset of individuals may experience a second, less severe, late-phase reaction several hours after the initial activity (Virant, 1992).

EIB was first noted in people with asthma, but now is known to occur in patients with allergic rhinitis, atopy, cystic fibrosis, and even in some with none of these underlying conditions. In the past, EIB was seen to be problematic more in the young, however, given the recent emphasis on the benefits of wellness and fitness in the older populations, EIB has become an issue for all ages (Hendrickson, 1993). The research presented in this thesis will focus on EIB in the asthmatic population.

### 1.1.3 Definition of asthma

Asthma is a Greek word meaning panting or shortness of breath. It is a protean condition that has withstood definition for centuries. As Gross (1980) says "(Asthma is) like love - we all know what it is, but who would trust anyone else's definition".

The 1996 Canadian Consensus Guidelines (CCG) adopted the following definition: "*Asthma is a disorder of the airways characterised by paroxysmal or persistent symptoms (dyspnea, chest tightness, wheeze and cough), with variable airflow limitation and airway hyperresponsiveness to a variety of stimuli. We believe airway inflammation (including mast cells and eosinophils) or its consequences is important in the pathogenesis and persistence of asthma. This provides a strong argument for the recommendation that the management of asthma should focus on the reduction of this inflammatory state through environmental control measures and the early use of disease-modifying agents, rather than symptomatic therapy alone.*"

Asthma affects approximately 5 to 10 % of the Canadian population (Boulet, 1994). The clinical features result from inflammatory changes in the bronchial airways that induce bronchial hyperreactivity (BHR). Increased BHR causes an exaggerated bronchoconstrictor response to various provoking stimuli such as allergens, environmental irritants, viral respiratory infections, cold air, and exercise. EIB appears to be a specific manifestation related to the degree of underlying bronchial reactivity (McFadden, 1994). The prevalence of BHR is highest in asthmatics, but may, as stated above, be independent of asthma and associated with other conditions (Levy & Hilton, 1993).

### 1.1.4 Prevalence of EIB

Because the prevalence of the major predisposing conditions, asthma, atopy, and rhinitis, is high, EIB is common. Sixty to 90% of people with asthma experience EIB and consider exercise a major trigger of their asthma symptoms (Rupp, 1996). Indeed, some claim that all asthmatics will experience EIB if hyperventilation and increased minute volume are of a high enough level (Mehta & Busse, 1997). In a study by Kawabori (1976), 41% of allergic children without asthma demonstrated EIB, and in general, other studies have found the prevalence in allergic rhinitic individuals to be around 40 to 50% (cited in Nastasi, 1995). The prevalence of EIB is somewhat lower in studies involving a general population with no history of asthma or allergy. Rates in

this group vary from 6% to 13%, with a slightly higher incidence in children and young adults, supposedly because children are more active (Randolf, 1997).

EIB gained considerable attention after the 1972 Olympic Games when a gold medalist in swimming had his medal rescinded because he took oral ephedrine prior to the race to control his EIB. Since then, several incidence/prevalence studies have been conducted among athletes with results in the 3 to 14% range (Mehta & Busse, 1997). Screening studies conducted on five Australian Olympic teams demonstrated a prevalence rate as high as 14% (Huftel, 1991), while US studies on the 1984 Olympic team demonstrated that 11% (67 of 597) had EIB (Pierson & Voy, 1988). Mannix et al. (1996) described EIB among professionally coached figure skaters. They measured FEV1 before and after a long program on 124 skaters and found that 43 (35%) had a drop of ≥ 10% in FEV1, 19 (15%) of these 43, had a drop of ≥ 15%, and only eight were known asthmatics. Provost-Craig et al. (1996) found an overall rate of 30% in a similar but younger population.

In a study to evaluate undiagnosed EIB in high school athletes, Rupp et al. (1996) identified an incidence of 17% in those at risk (based on histories) and 12% in those with no risk for EIB. Another group, with the same objective, exercise challenged 65 students and found that 66% demonstrated a significant drop in airflow (Shield, 1991). The wide variation in these figures may be due to the differences in the selection criteria used to identify the population to study. The presence or absence of one or more of the predisposing conditions is a critical issue, as are other factors described in section 1.1.7.

### 1.1.5 Time course of an episode of EIB

Most people experience bronchodilation during physical exertion due to an increase in circulating catecholamines (Stirling, 1983). At the completion of strenuous exercise (i.e. a workload of roughly 80% of maximal oxygen consumption, or 70 to 80% of the person's maximum predicted heart rate, for a minimum of five to eight minutes),

individuals with EIB experience a phase of bronchoconstriction that can begin almost immediately and progress until it peaks in three to fifteen minutes. This phase is followed by slow resolution to pre-exercise airflow patterns over a period of 20 to 60 minutes (Godfrey & Bar-Yishay, 1993). Uncommonly, a late phase of constriction might be experienced 4 to 12 hours after the initial exercise. When it does occur, the second episode is generally less severe than the earlier response, but the magnitude of the second is positively correlated with the first. There is no one factor that can predict who will have a late response, and it does not happen consistently to the same individuals (Virant, 1997). The clinical importance of the second response remains a matter of controversy.

There are wide variations in the nature and severity of EIB episodes, and the more severe responses should not be taken lightly. In *Asthma and Exercise*, Jackie Joyner-Kersee, an Olympic sprinter and asthmatic, describes a near death experience that she attributes to her denial of the condition and a reluctance to take her prophylactic medication (Hogshead, 1989). When a person has an exacerbation of asthma or heightened bronchial hyper-reactivity, even minimal exertion can induce severe EIB (Anderson, 1997). Antigens, air pollutants, or respiratory viruses, can all increase bronchial lability and exercising while exposed to these stimuli can provoke a severe reaction in those who are susceptible (Rupp, 1996). Exercise-induced anaphylaxis has been reported (Hendrickson, 1993). 'Rescue therapy', medications known as $\beta_2$ agonists, are effective in reversing the bronchoconstriction, and should be readily available and used. Anderson (1975) states that a fall in FEV1 or PEFR of 25 to 30% may require reversal. It is incumbent upon the adults who supervise physical activities to be knowledgeable about EIB and the treatment for it. Also, people who suffer EIB need to be educated to remain in the company of others until the episode is resolved.

Fortunately, most episodes resolve spontaneously within one hour, recovery being defined as air flow returning to within 10% of baseline values (Anderson, 1975).

Approximately 40% to 50% of individuals who have an initial episode of EIB followed by spontaneous recovery, will show a 'refractory period'. A refractory period is defined as 'the period of diminished responsiveness when a second period of exercise follows the initial exercise in under 2 hours (Randolf, 1997). During these two hours, an identical exercise task may still reduce FEV1 but to less than 50% of the drop measured in the initial test (Anderson, 1985). Refractoriness is somewhat illusive as it can be present at some times and not at others. The cause of the refractory period is not fully understood, but it has been suggested that it may be caused by prostaglandins. It has been observed that the refractory period can be inhibited by indomethacin, which is an antagonist of prostaglandins (O'Byrne, 1986).

### 1.1.6 Impact of EIB on the quality of life

Asthma is well known to cause a significant deterioration in the quality of life (Price, 1994). The threat of an asthma attack leads to withdrawal from physical exertion and social activities, which can create an altered sense of self-esteem (Padur, 1995). Children don't want to be labelled as a malingerers, be stigmatised, or be the last ones to be chosen for a team because of physical limitations, especially one such as asthma, which may not be an obvious impairment (Perrin, 1992). Teenagers may deny the condition because they fear restrictions on their participation in sport (Nastasi, 1995). Athletes too, tend to minimise or deny symptoms out of a sense of embarrassment or simply a lack of understanding of what they are experiencing (Randolf, 1997; Hogshead, 1989). The literature does not specifically separate the impact of suffering with EIB from the impact of having asthma, however the two are intricately entwined. The presence of EIB is problematic for physical and psychological reasons too, since like asthma, it is variable and somewhat unpredictable. The fear of sudden breathlessness creates a sense of panic and prevents many children from participating and parents may even impose restrictions (Butz, 1993). The fear of failure, or of delivering a sub-optimal performance leads to a reticence to become involved, with the result that many opt to be sedentary (Hogshead, 1989). This is most unfortunate, for involvement in sport and exercise is beneficial for several reasons. It has been shown that when asthmatics improve their aerobic fitness, they improve their tolerance to

physical effort and increase the threshold at which EIB will appear, thus fit people cope better with the same degree of airway obstruction than unfit people (Aborelius, 1984; Rufin, 1997).

EIB is the most common respiratory problem seen in either recreational or competitive sports (Mehta & Busse, 1997). It creates special problems for numerous accomplished athletes (Pierson, 1988; Hogshead, 1991). They experience a frustration because the body is neither predictable nor reliable and it may disappoint them during a crucial competition. If untreated, EIB can severely hamper athletic performance (Hogshead, 1989). The prevalence studies conducted among athletes indicated that EIB was both common and under-diagnosed. Unfortunately, the symptoms of EIB are often perceived as a normal consequence of vigorous exercise. In the book, Asthma and Exercise, (1989) Olympic swimmer Nancy Hogshead writes "*I would sometimes feel unusually winded and tired during my workouts and competitions. After some particularly hard training session or race, it wasn't uncommon for me to pass out momentarily at pool-side or have my face turn purple from exertion. I regarded this as normal... after all, pushing yourself to the limit will often leave you breathless. My coaches thought it was terrific when I passed out and they praised my 'toughness'. All the while I associated my heavy breathing with 'not being in shape'. I attributed most of my difficulties to physical or mental training defects and scolded myself for not working hard enough in practice or for not being tough enough at the end of a race. It never occurred to me that my breathing problems were linked to asthma. None of the coaches I trained with or physicians who examined me ever indicated that I had a special breathing problem.*"

Many competitive people, Jackie Joyner-Kersee among them, will deny the problem and struggle on unnecessarily. Some worry about drug testing and being accused of doping or of using a performance enhancing agent; still others dislike having to openly rely on medications, or having to notify colleagues and authorities in a society that

emphasises independence (Price, 1994). There is a sense of lost control, a sense of inadequacy, a sense of being cheated (Hogshead, 1989).

### 1.1.7 Factors that affect severity

There are several factors that can affect the severity of an attack and these must be standardised in order to obtain unbiased answers. The variation in rates quoted previously may reflect differences in underlying risk of EIB in the selected population, the selected definition of EIB (i.e. a ≥10% or ≥ 15% fall in air flow), the variations in environmental conditions, the duration and intensity of the exercise challenge itself, or differences in how outcomes were measured. Table 1.1 outlines the effect of potential effect modifiers.

**Table 1.1 Factors that influence the severity of EIB**

| | Decrease EIB | Increase EIB |
|---|---|---|
| **Environmental conditions** | Warm temperatures (34-37 °C), high humidity (100%)[1]<br>Absence of aeroallerogens<br>Low air pollution | Cold temperatures, dry air[1]<br>Airborne particles and pollutants[2]<br>allergens, moulds, dust<br>irritants e.g. automobile exhaust, sulphur dioxide, nitrogen dioxide, smoke, ozone |
| **Type, intensity, duration, of exercise** | Short episodes of fast/slow running with brief rests [5]<br>$VO_2$ max < 40% predicted[3]<br>< 3 minutes continuous exercise[4] | Continuous activities that require near maximum aerobic capacity [5]<br>$VO_2$ max ≥ 60% predicted [3]<br>6-8 minutes continuous exercise [4] |
| **Overall control of asthma and BHR** | Good control: FEV1 > 70% predicted<br>↓ BHR | Poor control: FEV1 < 65% predicted<br>↑ BHR[6] |
| **Physical conditioning** | Good physical conditioning,<br>Warm-up and cool down sessions | Poor physical conditioning,<br>Sudden burst of activity<br>Fatigue[2]<br>Emotional stress[2]<br>Athletic overtraining[2] |
| **Respiratory tract infections (RTI) especially viral** | No RTI | Presence of RTI[2]<br>Sinusitis[6] |
| **Time since last exercise** | If within last 40 - 90 min may benefit from refractory period (tachyphylaxis)[6] | More than 2 - 3 hours |
| **Current medications** | Maintenance antiinflammatories<br>Bronchodilator medication | Salicylates, NSAIDS, beta-blockers[6] |
| **Pre exercise foods eaten** | | Peanuts, celery, shrimp, grain, carrots, bananas[6] |

[1] Deal 1980; [2] Mellion, 1992; [3] Airway obstruction reaches a plateau when maximum oxygen uptake ($VO_2$ max) reaches 75% (Wilson, 1981); [4] Longer periods up to 32 min. do not increase bronchoconstriction (Morton, 1983); [5] Morton, 1982; [6] Hendrickson, 1993;

### 1.1.8 Diagnosis

The information needed to make a diagnosis of EIB can usually be elicited by taking a thorough history. Clinical suspicion should be aroused when patients, who may have otherwise good lung function, complain of shortness of breath (SOB) and symptoms

such as cough, wheeze, chest pain, or prolonged recovery time following exercise. Coaches and trainers should be aware of 'locker room cough', of athletes 'being winded' or of appearing 'out of shape' despite vigorous conditioning. The types and level of exercise that cause the symptoms are important; running, cycling, and dancing are more asthmogenic than walking for instance (Hendrickson, 1993). If symptoms are relieved by inhaling a $\beta_2$ agonist, or if symptoms are prevented by taking a $\beta_2$ agonist before exercise, then a diagnosis of EIB is supported (McFadden, 1994). According to Anderson (1997), symptoms are rare with mild EIB, and so the presence of SOB, wheezing, chest tightness, etc. suggest a fall in lung function of at least 20%.

People with EIB often have normal lung function at rest (Hendrickson, 1993). Clinicians should be aware that highly trained athletes often have above average resting lung function (i.e. well above predicted normal values for age, height, sex and ethnic group) but can, and do, exhibit significant bronchoconstriction that is problematic for that individual (Rupp, 1996). When the history suggests EIB, a definitive diagnosis can be made using objective measures of lung function, collectively called pulmonary function tests (PFTs). From the spectrum of PFTs available, most clinicians and laboratories use the measures of FEV1 or PEFR to quantify EIB, with FEV1 being favoured (Anderson, 1995). FEV1 is measured using a spirometer, an expensive instrument with some computer capabilities. The manoeuvre to produce the FEV1 and other PFTs is effort dependent and one advantage of a spirometer over a peak flow meter, is that the machine will indicate whether a sufficient effort has been supplied to give a valid reading. The PEFR is measured using a peak flow meter, a hand held plastic instrument that can be purchased in most pharmacies. The advantages of measuring the PEFR are that it is less expensive and is more easily performed under field conditions. The disadvantage is that this measure is entirely effort dependent and people must be taught and observed to use proper technique to obtain a valid reading.

Vigorous exercise can cause a decrease in airflow of 7 to 9% even in normal persons, but a decrease in FEV1 of 10% from baseline has been shown to represent a change greater than two standard deviations away from the normal response (Kattan, 1978). Based on this finding, a decline of ≥ 10% in FEV1 or PEFR has become the minimum criterion for the diagnosis of EIB. By consensus, the diagnostic scale is: post-exercise decreases of 10% to 20% in FEV1, or in PEFR indicate mild EIB, 20% to 40% represent moderate, and ≥ 40% represent severe EIB (Eggleston, 1984).

### 1.1.9 Exercise Challenge Testing

Whether formal exercise testing is used to diagnose EIB, to assess the effect of chronic therapy on the control of asthma, or to determine the effect of prophylactic therapy on EIB, the protocol for the challenge is important. Before testing, medications that could influence the EIB response should be withheld. The following periods of abstinence apply: short acting antihistamines, 48 hr.; long acting antihistamines, 1 wk.; sustained release oral bronchodilators, 24 hr.; short acting $\beta_2$ agonists, sodium cromoglycate, and nedocromil sodium, 6 hr.; long acting $\beta_2$ agonists and theophyllines, 24 hr.; corticosteroids either aerosol or oral should not be taken the morning of the study. In addition, caffeine should be avoided and the person should not have exercised earlier in the day. Resting FEV1 should be ≥ 75% of predicted values (Anderson, 1995).

*An appropriate exercise protocol in a laboratory includes:

1. Equipment: Either a motor-driven treadmill or a cycloergometer is required.

2. Environmental control: Room temperature should be kept around 23 °C. Sometimes it is reduced to subzero temperatures. The relative humidity should be kept under 50%.

3. Physical intensity: This is determined by the individual person's response based on age, size, and physical fitness, and is measured by objective criteria such as ventilation

rate (between 40 to 60 % of the predicted maximum) or heart rate (between 85 to 90% of predicted maximum).

4. Duration of exercise: Continuous effort for 6 to 8 minutes breathing through the mouth is needed to trigger an EIB response.

5. Outcome measures: Either of FEV1 or PEFR, must be determined pre-exercise and at 5 minute intervals for 20 to 30 minutes post-exercise.

(*Eggleson, 1984)

### 1.1.10 Quantifying EIB

The traditional way to quantify EIB is to express the maximum reduction in FEV1 or PEFR that occurs after exercise as a percentage of the pre-exercise value. The result is called the percent fall index (maximum % fall FEV1 or maximum % fall PEFR). It is obtained using the following formula: (PFT refers to either FEV1 or PEFR.)

$$\text{maximum \% fall PFT} = \frac{\text{pre-exercise value - lowest post-exercise value}}{\text{pre-exercise value}} \times 100$$

Exercise testing is highly specific for EIB and positive results provide good assurance of the presence of the condition. The Canadian Consensus Guidelines and the American Thoracic Society state that a 12% change in FEV1 is clinically significant (CCG, 1996; ATS, 1993).

In addition to being a diagnostic test, an exercise challenge is frequently used to monitor the effect of chronic asthma therapy. For this purpose, it is useful to plot the pre and post exercise values as a percentage of the predicted value expected for the age, height, sex, and race, or the individuals 'personal best' lung function. Over time, with anti-inflammatory therapy, the individual's general lung function can improve, yet the percent fall index can remain the same. Studies have indicated that despite

adequate therapy for chronic asthma, some people still suffer from EIB on vigorous exercise (Anderson, 1995).

When determining a course of EIB management, it is useful to know the acute or immediate effect of an active drug that is used prophylactically. The protection afforded by a drug is calculated by comparing the active drug response with the placebo response (Boner, 1988), to determine whether or not the drug provided clinically significant protection against EIB. Protection values ≥ 50% are regarded as clinically significant (Anderson, 1995). A protection index is calculated using the following formula:

$$\% \text{ protection} = \frac{\text{max \% fall placebo - max \% fall treatment}}{\text{max \% fall placebo}} \times 100$$

## Section 2: History, Etiology and Treatment of EIB

An understanding of the pathophysiology involved in EIB is helpful when planning treatment, but the exact mechanism of EIB is multifactorial, complex and not completely understood. No unifying concept on the pathogenesis has been accepted, and the rapid accumulation of new knowledge of inflammation and immunology has lead to some confusion (Hendrickson, 1993).

### 1.2.1 History of EIB

In 150 AD, Aretaeus wrote, "*If from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called asthma...*". He also made some interesting observations relating to the pathology of EIB... "*The cause is a coldness... of the spirit. There is a postponement of death to those in whom the lungs are warmed and heated in the exercise of their trade, from being wrapped in wool such as the workers in gypsum, or braziers, or blacksmiths, or the heaters of baths.*" (cited in

Virant, 1997). The next significant writing on EIB was not for 1500 years, in the late 17th century, when Sir John Floyer, an English physician and himself an asthmatic, reported that different types of exercise caused differing amounts of EIB (ibid). Another English physician, in the mid 1800s, observed that exposure to cold air exacerbated the response (Sly, 1986).

It was not until 1962 that Jones and colleagues reported that the severity of EIB was dependent on the duration of activity. Then in the early 1970s Chan-Yeung et al (1971), recognised that the severity of EIB was associated with the level of ventilation. These observations led to studies that compared different types of exercise, of similar intensity, on the degree of EIB experienced. Free range running was found to be the most potent catalyst, followed by running on a treadmill, cycling, swimming, kayaking, and then walking (Fitch, 1976). Many of these historical ideas have been merged with modern research to be either modified or disproved (Godfrey & Bar-Yishay, 1993).

### 1.2.2 Current thoughts on etiology

Over the last thirty years there has been extensive research investigating the potential factors that might stimulate EIB and influence the severity of it. There is no consensus, but the most agreed upon factors include respiratory heat loss, water loss, or both, that are associated with airway re-warming and humidification of large volumes of air during hyperventilation. Several inflammatory mediators and reflex vagal responses have been implicated as well (Anderson, 1995).

Two somewhat opposing hypotheses have emerged as possible mechanisms that cause airway narrowing. One hypothesis, sometimes referred to as the 'heat-flux hypothesis' (McFadden, 1986), suggests that excessive vasodilatation during airway rewarming and humidification (conditioning) causes vascular engorgement, thus reducing airway calibre. The other hypothesis, the 'water-loss theory', suggests that during

conditioning there is a loss of surface water in the mucosa and the remaining fluid becomes hyperosmolar. The increase in osmolarity stimulates mediator release, which stimulates bronchospasm, and consequently airway obstruction (Anderson, 1985a ). The rate and depth of ventilation appears to be a critical factor in either theory. Increased ventilation (minute ventilation) pushes the conditioning process down into the lower airways (McFadden, 1994). When airways of the $10^{th}$ generation and beyond become involved, the bronchoconstrictor response is triggered (Anderson, 1997).

**i. Heat-flux hypothesis**

In normal nasal breathing, inspired air is heated to body temperature and 100% water saturation in the first few generations of airways. This exchange of heat and water cools the bronchial mucosa. Hyperventilation during and after intense exercise greatly increases minute ventilation and thus a larger volume of air requires heating and humidifying. The nose is unable to condition the increased volume, particularly in people who switch to mouth breathing or have nasal congestion. This puts an added burden on the lower airways to condition the air (reactive re-warming), which results in a compensatory increase in bronchial circulation and mucosal edema. According to the heat-flux hypothesis, it is the vascular engorgement (hyperemia) and edema that are responsible for airway obstruction, rather than bronchospasm (Deal, 1979, 1980; McFadden, 1986, 1994). Asthmatics may have a greater reactive component than normal people because of hypertrophied and hyperplastic bronchial capillary beds which allow greater leakage of fluid into the airways and exacerbate the edema (McFadden, 1990). This became a well accepted theory. The problem remained, though, that some people still exhibited EIB under physiologic conditions (Anderson, 1985) and the heat-flux theory could not explain the refractory period during which, again there is heat loss, but relatively little bronchoconstriction.

**ii. Water-loss theory**

Experiments by Anderson in the 1980s suggested that the stimulus for bronchoconstriction was related to water loss from the airway mucosa while

simultaneously bringing large volumes of air to full saturation in a short period of time. The loss of water (periciliary fluid) from the airways produced a hyperosmolar environment. Hypertonicity may initiate degranulation of pulmonary mucosal mast cells with the subsequent release of several inflammatory mediators including histamine, leukotrienes, prostaglandins, platelet-activating factors, and neuropeptides from sensory nerves. The released mediators are believed to act in a number of different ways. First, they may stimulate bronchial smooth muscle spasm and thereby increase airway resistance. Second, they may cause reflex vagal bronchoconstriction via stimulation of irritant nerve receptors, or third, they may exert a chemotactic effect, attracting circulating neutrophils, which promote an inflammatory response (Anderson, 1985b). Edema from engorged capillary beds (the source of periciliary fluid) amplify the obstruction and decrease FEV1 (ibid). The effectiveness of $\beta_2$ agonists in preventing and rapidly reversing EIB support the claim of bronchial smooth muscle contraction. Mast cell release of late-phase chemotactic factors for eosinophils, neutrophils, and mononuclear cells could explain the inconsistent inflammatory phase that some people experience three to eight hours later (Anderson, 1985b). To further support the water-loss theory, studies with inhalations of hyperosmolar solutions have induced bronchospasm (ibid).

To date, it has been difficult to detect the levels of chemical mediators present before and after exercise, but support for their role in EIB may be partially explained by the relieving effects that different medications exert (Anderson, 1997; Hendrickson, 1993). For example, leukotriene $D_4$, one of the released mediators, is a potent bronchoconstrictor. Manning et al. showed that a leukotriene $D_4$-receptor antagonist can attenuate but not eliminate EIB (Mahler, 1992). Nedocromil sodium and cromolyn, both known mast cell stabilisers, inhibit EIB (Anderson, 1993).

In summary, the current understanding is that airflow obstruction caused by exertion may be related to both heat and water loss that trigger bronchospasm and mast cell

mediator release. Hyperventilation in cold, dry air would exacerbate the severity of EIB because of its potential to increase the surface area over which water loss occurs. This would lead to wide spread periciliary fluid hyperosmolarity, mast cell degranulation, and also stimulate dilation of the bronchial capillary beds recruited to rewarm the colder air, therefore both heat and water loss would contribute to a greater degree of obstruction (Virant, 1997).

### 1.2.3 Treatment

EIB can be successfully managed in the majority of cases. Exercise in itself, only serves to increase minute ventilation so there are no specific activities that people should avoid (McFadden, 1994). In discussion with athletes, parents, and coaches, clinicians should emphasise that EIB is not a medical condition nor a criterion for exclusion from sports (Kyle, 1992). The goal of treatment is to prevent or, at least, to reduce the severity of EIB so that the individual can participate without serious respiratory limitations. The goal is achieved through a combination of patient education, a commitment to fitness, pharmacologic intervention, and employing a number of nonpharmacologic strategies (Mahler, 1993). Garfinkel and colleagues (1992) analysed the results from an exercise questionnaire given to asthmatics, and found that those with mild to moderate asthma may perceive their disease as a limiting factor to improving fitness, and that they lacked knowledge about asthma and exercise (cited in D'Urzo, 1995). Clinicians have a responsibility to provide education and encourage anyone with EIB to engage in regular physical activity. When discussing management with athletes, it is important to recommend drugs that would be allowed by athletic governing bodies.

There are different pharmaceutical compounds that can provide at least partial relief from EIB and that appear to operate on different phases of the EIB response (Freed, 1995). The traditional favorite has been the short acting $\beta_2$ agonist, followed by sodium cromoglycate (SCG), a mast cell stabiliser. Recently, nedocromil sodium (NCS), a new mast cell stabilising agent has shown promise (McFadden, 1994). When

neither of these medications, given singly or in combination, are sufficient, then anti-cholinergics, and theophyllines can be added. A leukotriene receptor antagonist, (zafirlukast) introduced in late 1997, has shown beneficial results in a select population (cited in Mahler, 1993). Each of the treatment regimens has a variable clinical effect. As mentioned, a combination of drug and non-drug therapy may be necessary (Spector, 1997). Table 1.2 outlines the more common drug therapies with their advantages and disadvantages.

**Table 1.2 Single dose, prophylactic drug therapies for exercise-induced bronchoconstriction**

| Drug | Action | Route of Administration | Advantages | Drawbacks |
|---|---|---|---|---|
| *$\beta_2$ agonist: Short acting eg. albuterol, terbutaline, salbutamol | -bronchodilation<br>-reverses bronchospasm | inhaled<br>oral | -can inhibit EIB<br>-can reverse EIB<br>-fast action - 5-15 min.<br>-duration varies 3 - 6 hours<br>-effective in 85 - 90%<br>-no ergogenic effect[1] | -skeletal muscle tremors<br>-nervousness<br>-vasodilation<br>-decreased efficacy with frequent use (tachyphylaxis)[2]<br>-tachycardia<br>-oral not as effective** |
| *$\beta_2$ agonist: Long acting: e.g. salmeterol | -bronchodilation | inhaled | -duration up to 12 hours in 55%[3] | -slow onset<br>-cannot use more than 2 puffs q 12 h.<br>-may blunt rescue action of short acting $\beta_2$ agonist<br>-not for long term use[5] |
| *Sodium Cromoglycate (SCG) | -stabilises mast cells<br>-anti-inflammatory | inhaled | -fast action: 10 - 45 min<br>-few side effects<br>-inhibits early and late EIB<br>-can combine with $\beta_2$ agonist for ↑ effect | -more effective in children<br>-need high doses<br>-no bronchodilator effect<br>-study results vary on effectiveness |
| *Nedocromil sodium (NCS) | -stabilises mast cells<br>-anti-inflammatory<br>-may protect nerves from effects of hyperosmolarity[6]<br>-inhibits $Cl^-$ influx | inhaled | -fast action - 15 min<br>-few side effects<br>-adults and children<br>-inhibits early and late phase EIB<br>-effective against fog, aeroallergens, pollution,<br>-can combine with $\beta_2$ agonist for ↑ effect | -some perceive a bad taste<br>-no bronchodilator effect |

continued on next page...

**Table 1.2 continued... Single dose, prophylactic drug therapies for exercise-induced bronchoconstriction**

| Drug | Action | Route of Administration | Advantages | Drawbacks |
|---|---|---|---|---|
| *Theophyllines | -long-acting bronchodilation | oral: syrup or tablet | -prolonged duration<br>-add only if other therapy not satisfactory[1] | -slow onset 1 - 2 hr.<br>-narrow therapeutic range (serum levels)<br>-several side effects<br>-potential toxic effects<br>-other medications affect serum levels |
| Ipratroprium bromide | -anti-cholinergic (relieve bronchospasm)<br>-modest bronchodilation | inhaled | -can be added to SCG, NCS, $\beta_2$ agonists, if difficult to control EIB | -slow onset: 1 - 2 hr.[5]<br>-variable effectiveness[1]<br>-effective in 30-40%<br>-not first line therapy |
| leukotriene antagonists zafirlukast | antagonise leukotrienes | oral | early studies show some benefit in EIB | -released 1997<br>-side effects |
| **epinephrine: isoproterenol ephedrine | bronchodilation | oral injection | quick relief in severe allergic reaction and severe asthma attack | -short duration<br>-potent side effects |
| *antihistamine: e.g. terfenadine, astemizole, ketotifen | -improve nasal function<br>-↓ bronchospasm | oral | -can inhibit EIB up to 35% | -variable response rates[4] |

*These pharmacologic agents can be utilised in both national and international competition when approved by the appropriate national governing body and/or the US Olympic Committee and the International Olympic Committee.

** These agents are not permitted in international competition

[1]Mahler, 1993; [2]Cheung 1992; [3]Kemp, 1994; [4]Finnerty, 1990; [5]Randolf, 1997; [6] Anderson, 1993;

EIB is a disease of the airways and treatment delivered via the inhaled route is generally preferred (Paton, 1995). The inhalation route offers several advantages: rapid onset of action, restricted local effect, smaller dose requirements, and fewer systemic side effects (Paton, 1995). There are a number of inhalant devices on the market, but by far the most common are metered dose inhalers (MDI) that deliver a prescribed dose of drug via an aerosol spray. Careful and proper technique must be taught and followed in order to obtain maximum deposition of drug deep into the airways. Spacer devices can be attached to an MDI to enhance dose delivery and eliminate some of the finer co-ordination and timing skills needed with the MDI alone (Crompton, 1995).

The main determinants of the severity of EIB involve the overall control of asthma and the underlying BHR (Randolf, 1997). The first step in managing EIB then, at least among asthmatics, is to achieve and maintain control of their asthma through regular monitoring and adequate medication. When the underlying bronchial hyperreactivity is not sufficiently managed, almost any form of activity and fluctuation in temperature and humidity will exacerbate EIB (McFadden, 1994). The current Canadian Consensus Guidelines (1996) suggest daily use of inhaled corticosteroids or non-steroidal anti-inflammatory drugs to control bronchial inflammation in symptomatic asthma. This approach has been shown to reduce the severity of EIB over time (Henriksen, 1985), but not necessarily to eliminate it (Vathenen, 1991). If lung function is within normal limits, single doses of inhaled NCS or SCG before exercise, will control EIB (Anderson, 1997). Anderson recommends NCS or SCG be used as first line treatment over $\beta_2$ agonists, and that the latter be reserved for rescue therapy when required. Anderson (1997) also suggests that when airflow limitation is below 75% of predicted values before exercise, a $\beta_2$ agonist should be taken. If the FEV1 or PEFR does not improve to at least 75% of predicted normal values, the person should not exercise at that time.

It is important for patients and supervisors to know how to treat EIB when it occurs, particularly when it does not resolve spontaneously. It can be dangerous for a person to continue to exercise when lung function is decreasing. Should an individual feel an asthma attack coming on during exercise, it is almost certain that it will worsen on cessation (Anderson, 1997). For most people, mild to moderate EIB can be reversed quickly by inhaling one puff of a short acting $\beta_2$ agonist every 1 to 2 minutes for up to three puffs. For severe attacks, as many as 10 or more puffs can be given while help is being summoned (CCG, 1996). Since the peak severity of an attack usually occurs 3 to 15 minutes post exercise, it is advisable to monitor children or adults for longer. They should not be allowed to leave the area unaccompanied, until the episode has resolved and one is assured of a spontaneous recovery.

### 1.2.4 Non-pharmacologic methods to prevent EIB

Education in regard to additional non-pharmacologic strategies of managing EIB will help to augment drug therapy. These, however, should not be used exclusive of medication according to Pierson, who serves as co-director of the Exercise-induced Bronchospasm Project sponsored by the US Olympic Committee and the American Academy of Allergy and Immunology Sports Medicine Committee (Hogshead, 1989). Katz agrees that the nonpharmacologic approaches will not eliminate EIB, but certainly are useful, and are an alternative for those reticent to taking drugs (Hogshead, 1989). Table 1.3 outlines the non-pharmacologic strategies that some find useful.

**Table 1.3 Non-pharmacologic management of EIB**

| Strategy | Suggestions |
|---|---|
| **Physical conditioning** | If not already fit, improve aerobic fitness to decrease ventilation rate required for intense exercise[7] |
| **Warm up period** | Low level exercise for 20 min. before main exercise[2] or multiple short bursts of activity separated by intervals of recovery[8,9]<br>Induce a refractory period prior to big events[5] |
| **Environment control** | Exercise in warm, humidified air[4]<br>Avoid exercising in areas of high air pollution (e.g. near ↑ traffic area, during pollution alerts)<br>Avoid exposure to allergens, (e.g. during pollen alerts)<br>Choose an indoor activity when necessary |
| **Equipment** | Wear a face mask to encourage re-breathing warmed, humidified air[1] in cold weather and to screen out aeroerallergens |
| **Other helpful hints** | Breathe through the nose rather than mouth when possible<br>Avoid hyperventilating<br>Avoid shellfish, peanuts, celery, carrots, bananas before a workout[3] |

[1]Brenner,1980; [2]Mahler, 1993; [3]Eggleston, 1984; [4]Katz, 1986; [5]McFadden, 1994; [7]Henriksen, 1983; [8]Morton, 1982; [9]Schnall, 1980

**Summary**

EIA is a condition that causes problems within a broad segment of the population suffering with asthma and allergies. It can interfere with the daily physical activities around the home and at work, as well as compromise efforts in recreational and competitive sport. The signs and symptoms of cough, chest tightness, breathlessness, and wheeze, typically occur when the exercise is over, but they can develop during exercise and limit performance. It is important to remember that severe EIB can occur in people with good and even better than average lung function at rest, and that resting lung function cannot predict the amount of therapy that will be required to inhibit the EIB response (Anderson, 1997). EIB can still occur, even when chronic management of lung function is adequate, and so it remains clinically important to find safe and effective therapy as a adjunct to regular care. The $\beta_2$ agonist medications afford acute relief from bronchospasm but do not attack the other mechanics involved in EIB. For this reason researchers are concentrating on other pharmacologic agents that will

prevent EIB (Anderson, 1993). One such agent is a newer compound called nedocromil sodium that is discussed in the following section.

## Section 3: Nedocromil sodium

### 1.3.1 Background

Nedocromil sodium (NCS) is a non-steroidal, anti-inflammatory drug introduced into Canada in 1990 and sold under the trade name of Tilade® (Rhone-Poulenc Rorer, Canada Inc.). It is approved for the treatment of chronic, mild to moderate asthma in patients 6 years and older. NCS is a water soluble disodium salt of pyranoquinoline dicarboxylic acid, a compound that is distinct from other currently available asthma medications and suitable for topical administration to the bronchial airways by inhalation (Auty, 1986). The exact mechanism of action is not known, but it appears to have beneficial effects on several pathways involved in the asthmatic response (Keenan, 1994). NCS is a unique compound that was developed in response to the need for a drug that was more potent and more clinically diverse than a chemically unrelated but clinically and pharmacologically similar drug, sodium cromoglycate (Bernstein & Berstein, 1993).

### 1.3.2 Indications for use

According to the Compendium of Pharmaceuticals and Specialities (CPS, 1997), NCS is indicated for adjunct therapy in reversible airways obstructive disease, including asthma and bronchitis, particularly when allergic factors are present. It can be used safely with concomitant asthma therapy. Several studies demonstrate that NCS can prevent the early asthmatic response triggered by inhalation of allergens to which an individual is sensitive (Church, 1989). This property makes it an attractive drug for atopic individuals who exercise outdoors, especially in spring and summer when pollen counts are high. Other evidence shows NCS to effectively inhibit the late asthmatic response, which frequently occurs 6 to 12 hours after an early response in approximately 60% of atopic asthmatics (Holgate, 1986; Church, 1989; Rocchiccioli,

1989). The protective effect against the late response is observed even when $\beta_2$-agonists have prevented the early response. This observation adds to the attractiveness of the drug (Church, 1989). Daily use of NCS has shown to improve overall asthma symptom scores (Parish, 1993; Bernstein & Bernstein, 1993; Keenan, 1994).

A second indication, cited in the CPS (1997), is for episodic, or occasional use to attenuate bronchospasm provoked by sulphur dioxide, fog, atmospheric pollutants, aeroallergens, cold air, and exercise (Rocchiccioli, 1989).

The drug is marketed in an MDI that supplies 2 mg NCS in an aerosol mix with sorbitan trioleate, dichlorotetrafluoroethane, and dichlorodifluoromethane (propellants), per actuation. The recommended daily dose for maintenance therapy is 8 to 16 mg, but a single dose of 4 mg taken up to 30 minutes in advance, is recommended for occasional prophylactic use (CPS, 1997). Pre- and post clinical studies, together with subsequent clinical use have shown that NCS is well tolerated and has not shown to be toxic when given in doses up to 32 mg daily for 28 days (Auty, 1986).

The response to NCS does not appear to depend on the patient's age, race or atopic status (Auty, 1986). To date, studies in animals suggest there is no reason to suspect NCS would adversely affect human pregnancy, the fetus, or breast feeding infants. As yet however, safety in these areas in humans has not been established (CPS, 1997).

### 1.3.3 Side effect profile

NCS has the added advantage of a low toxicity profile (Church, 1989) attributed to its pharmacokinetic properties. The systemic bioavailability of inhaled NCS is low. Since a portion of all inhaled medications are swallowed due to deposition in the oropharynx or from muco-ciliary clearance from larger airways, this facet becomes an important

feature of the drug. Only a small amount of what is swallowed (2 to 3%) is absorbed by the GI tract into the circulation, where it reaches peak plasma concentrations in 20 to 40 minutes. The plasma half-life of NCS is approximately 1.5 to 2.0 hours (CPS, 1997) and peak levels fall roughly 90% within 8 hours, therefore there is no systemic accumulation of successive doses (Bernstein & Berstein, 1993). The remaining portion of drug that is swallowed is excreted, unchanged, in the faeces.

Few side effects have been reported and the ones that have include, an unpleasant taste (12.2%); headache (6%); cough (7%); throat irritation (5.7%); nausea (3.8%); vomiting (1.8%); dyspepsia (1.2%); and abdominal pain (0.9%) (CPS, 1997). These effects (except for taste) are usually mild and transient and Keenan (1994) states that only 2 to 3 percent of patients discontinue therapy due to these adverse effects.

### 1.3.4 Mechanisms of action

NCS is believed to have many mechanisms of action (Gonzalez & Brogden, 1987). One is to stabilise the membranes of inflammatory cells such as pulmonary mucosal mast cells, bronchial epithelial cells, and alveolar macrophages (Keenan, 1994). When mast cell membranes are stabilised, they do not degranulate and release histamines, leukotriene $C_4$, and prostaglandin $D_2$, all of which cause bronchoconstriction (Church, 1989). A second mechanism of action postulated, is that NCS inhibits the activation of neutrophils, eosinophils, and macrophages, thus curbing additional mediator release, subsequent inflammation, and by extension, inhibit the development of bronchial hyperreactivity (Church, 1989). Increased bronchial hyperreactivity influences the degree of EIB experienced.

It has been proposed that the action of nedocromil extends to protecting afferent nerve endings in the airways from the effects of hyperosmolarity. The drug may potentially improve water transport to the airways and protect the submucosa from dehydration by blocking the chloride ion transport across epithelial cells (Anderson, 1997). NCS

can also inhibit release of neuropeptides that are thought to irritate nerve endings and stimulate bronchospasm (Keenan, 1994).

### 1.3.5 Summary

Nedocromil sodium belongs to a new class of drugs that has unique anti-allergic and anti-inflammatory properties and has a very low side effect profile. It appears to work in adult and pediatric populations alike, through a variety of mechanisms which attenuate the signs and symptoms of asthma and bronchial hyperreactivity. Early trials show clinical promise but much remains to be learned about its place in the management of specific problems related to obstructive airways disorders.

# Chapter two

## Section 1: The Cochrane Collaboration

### 2.1.1 Introduction

Clinicians, responsible for helping people who have EIB develop treatment and management strategies, must decide when the scientific evidence is sufficient to recommend and adopt an approach. While patient perspectives and clinical experience are important components of evidence-based medical care, an integral part of the decision process involves searching for, and evaluating, primary research.

This task, although accepted, is time consuming and difficult due to the prodigious growth of information in biomedical journals. Furthermore, the published literature is of variable quality and the results reported are often discordant. To first identify the trials pertinent to a particular area of interest, and then to interpret the often inconclusive or conflicting results, requires training and skill in critical appraisal. Unfortunately, many health providers have neither the time nor the opportunity to acquire these important skills. An up-to-date, rigorously conducted, systematic review can be an attractive, efficient, and valid tool that captures the best available evidence and provides a comprehensive summary of the existing state of knowledge on a defined topic (Greenhalgh, 1997b).

### 2.1.2 A Systematic review

A systematic review is secondary, retrospective research that can be defined as the application of scientific strategies that limit bias in the systematic assembly, appraisal, and synthesis of all relevant studies addressing the same fundamental question (Ohlsson, 1994). There are a number of recent publications describing the rigor necessary to conduct a valid systematic review (Petitti, 1994; Mulrow & Oxman, 1997). Protocol requires that such reviews be based on an explicit question, a systematic search for the evidence, an unbiased selection of studies, and methods involving strategies that limit bias and random error (Chalmers, 1995; Greenhalgh,

1997). In following a comprehensive and systematic format, the review attempts to gain greater objectivity and generalisability to present readers with the best available evidence. Consequently, the result should be a valid representation of whether scientific findings are consistent, whether the results can be generalised across populations, settings, and treatment variations, or whether findings differ by particular subgroups (Mulrow, 1994).

### 2.1.3 A Meta-analysis

A meta-analysis is a statistical technique that integrates the quantitative results from the independent studies in a review into a single 'pooled' estimate of effect coupled with a measure of precision (Egger, 1997). Combining results across trials has the advantage of increasing the overall sample size, thereby increasing the statistical power to determine the presence or absence of a treatment effect (Mulrow, 1994). The approach has two advantages; first, it may unveil a significant effect from treatment when the individual trials are too small to reach statistical significance; and second, the pooled estimate provides the reader with an 'on average' measure of the overall effectiveness of interventions such as diagnostic tests, therapies or preventive applications (Jones, 1997).

When the results of individual trials have been combined into a pooled estimate, then a formal test for estimating the statistical probability of the observed differences being compatible is performed. The test used in a meta-analyses is a chi squared ($\chi^2$) test for heterogeneity. The test estimates the probability that the observed differences in results among combined studies occurred because of chance (Mulrow & Oxman, 1997). Should the $\chi^2$ result indicate that statistically significant heterogeneity exists, reviewers need to investigate the possible causes. Heterogeneity can stem from a variety of methodological decisions in conducting the review, or from differences among the studies themselves. A synoptic appraisal of discordant results is one of the strengths of a review (Cook, 1997).

The terms, systematic review and meta-analysis, are often used interchangeably, but this is not entirely correct. It is not always possible to calculate aggregate results (meta-analysis) from relevant studies (systematic review) because of variations in outcome reporting, or simply because the outcomes have nothing in common (Jones, 1997). The EIB review that forms the basis for this thesis does include a meta-analysis and so, despite this discrepancy, the terms meta-analysis, systematic review, and also overview, and review will be used synonymously in the remainder of the text.

### 2.1.4 The Cochrane Collaboration

The Cochrane Collaboration (CC) was founded in 1993 and is named after the late British epidemiologist, Dr. Archie Cochrane. He argued that the best available evidence about the effectiveness of medical therapy was contained in the thousands of randomised controlled trials (RCT) scattered throughout the biomedical literature that was not readily accessible to those who needed it for making decisions. Cochrane advocated a systematic process to locate the results from all relevant studies for each treatment, to summarise them for an overall conclusion in a systematic review, and subsequently, for the review to be regularly up-dated to include new evidence.

Today, the Cochrane Collaboration is an international, multi-disciplinary, volunteer network of clinicians (physicians, nurses, physiotherapists, and other health professionals), researchers (scientists, epidemiologists, biostatisticians, etc) and consumers, interested in health care delivery. All are committed to locating RCT's and other high quality evidence on the effects of health care, and to organise this evidence into systematic reviews.

The Collaboration offers support to 'reviewers' via Collaborative Review Groups (CRG). It is the mandate of the members of each CRG to produce and maintain reviews that will help furnish the 'best available evidence' for the treatment of conditions that reside within their particular scope of interest. One such CRG within the Collaboration, the Airways Review Group (ARG), conducts systematic reviews on topics including asthma, chronic obstructive lung disease, sleep apnea, pulmonary

embolism, rhinitis, and bronchiectasis. The author of this thesis is a member of the Airways Group, and the meta-analysis on which this thesis is based, was produced conforming to the explicit standards of the Collaboration and the editorial staff of the Airways Group.

Upon completion, a review is submitted to the respective Cochrane Review Group to undergo internal review by two editors, followed by external evaluation by at least one expert in the field. Once accepted, a review is published in a "module" of the Cochrane Library called the Cochrane Database of Systematic Reviews (CDSR). The Library is published by the BMJ Publishing Group in electronic form and updated quarterly.

The attributes of a Cochrane review are summarised in Table 2.1 and the Cochrane methodology is summarised in the text following the table.

**Table 2.1 A Cochrane Collaboration Systematic Review / Meta-analysis**

- information from a comprehensive search with selection bias minimised
- appraisal of relevant trials and appropriate statistical summary of all relevant outcomes
- conclusions about the effect of the intervention (benefits, harms) supported by the evidence
- recommendations for clinical application
- suggestions for further research
- reviews that are peer reviewed, respond to valid criticisms, and updated as new evidence becomes available
- reviews that are prepared by multidisciplinary, international teams
- accessibility through the electronic Cochrane Library issued quarterly and on the Internet through Synapse publications*
- Co-publication with peer reviewed journals

* subscription fee charged

### 2.1.5 Format of a Cochrane review

The objective for a systematic review is to provide an unbiased summary of the current evidence surrounding the effect of a health intervention. With this in mind, the methods employed to produce the review focus on data retrieved from randomised controlled clinical trials (RCTs), since this trial design is likely to provide the most valid information (Hennekins, 1987). The steps involved in preparing a review correctly require expertise in at least three areas; methodology, clinical knowledge,

and statistics (Bailar, 1997). It is recommended that reviews be a collaborative effort inclusive of these domains. Each step in the process of preparing a review is designed to ensure that the end product is reliable, reproducible, objective and as free from bias as possible.

The steps involved in conducting a Cochrane review are as follows:

**i. Formulate the research question**

The 'idea' for a review progresses to the formulation of a specific research question. This question is pivotal for focusing the review to ensure it is clinically relevant, sensible and answerable. The question must clearly define these four components: acceptable trial design, the population, the type of interventions or exposures vs. its control, and the outcomes of interest (Counsell, 1997). These delineations are then used to develop the inclusion / exclusion criteria for selecting studies for the review (Mulrow & Oxman, 1997).

**ii. Develop the protocol**

The written protocol provides not only a focus for the review but also serves as a permanent record of the a priori objectives and methods. The decisions made while preparing the protocol will help to reduce bias in the judgements required for identifying, selecting, and assessing studies for inclusion, and also when extracting data and analysing results (Mulrow & Oxman, 1997). Before embarking on a review, a protocol must be developed, reviewed and accepted by the editorial body of a Cochrane Review Group. Once approved, it is submitted to the Collaboration and published in the CDSR.

**iii. Identify eligible studies**

Unbiased and complete identification of relevant studies is of primary importance in assuring the validity of meta-analytic results (Dickerson, 1995). A comprehensive search should involve multiple overlapping strategies which could include:

- key-word searches of the computerised databases: MEDLINE, EMBASE, CINAHL, CURRENT CONTENTS or others that contain the body of

literature sought. This can be accomplished more quickly and efficiently through registers similar to the one developed by the ARG [1]

- scan references cited in relevant review articles, primary trials, and textbooks
- hand search relevant journals
- personal communication with experts and investigators in the field
- contact the manufacturer of the drug(s) under investigation
- search the Cochrane Controlled Trials Register (CCTR) within the Cochrane Library
- search Science Citation Index

Although there is no way to quantify the potential impact of language or publication bias on a review, which are criticisms often levelled against meta-analyses, attempts should be made to locate relevant trials regardless of language or publication status (Dickerson, 1995).

Once studies are located, the sequential task of selection and appraisal begins. Studies are selected for inclusion according to criteria arising from the question and the research objectives outlined in the protocol. Whether one or more reviewers is involved at this stage, the judgements made must nevertheless, be reproducible (Mulrow & Oxman, 1997).

**iv. Quality appraisal of included studies**

The validity of a trial depends upon the extent to which its design and conduct are likely to prevent systematic errors (Moher, 1995). There is no gold standard against which to judge the true methodological quality of a trial (Greenhalgh, 1997), and yet quality and design features are known to influence the results (Jadad, 1996). For example, studies using poor methodology have been shown to overestimate the treatment effect (Khan, 1996). Other specific features including

[1] To speed the search process for it's members, the Airways Review Group has developed an electronic register, with no language restrictions, that unifies all relevant records from the three largest on-line electronic databases, EMBASE, MEDLINE and CINAHL, in the areas of asthma, bronchiectasis, childhood wheezing, chronic obstructive pulmonary disease and sleep apnea from the inception of each database to 1998. The register is up-dated every six months and has been further supplemented by adding RCTs identified through hand-searching the top 20 respiratory journals. It thus provides a unique and extremely efficient means for identifying trials in respiratory health care. This register has been shown to retrieve 92% of the RCTs identified by handsearching two top respiratory journals from 1989 to 1993 inclusive. Its specificity is estimated to be 17% (Bara, 1995).

concealment of allocation (Chalmers, 1983; Schultz, 1995), blinding, and randomisation, have all been found to influence the effect size (Schultz, 1995). There is on-going research within Cochrane to establish empirical evidence for criteria believed to be important determinants of validity.

The Cochrane Handbook (1997) has identified four main sources of systematic error that can potentially bias trial results:

a) selection bias: systematic differences in comparison groups.
b) performance bias: systematic difference in the care provided independent of study intervention.
c) attrition bias: systematic difference in withdrawals.
d) detection bias: systematic difference in outcome assessment.

Selection bias can be avoided by using a randomisation scheme that will ensure that comparison groups are assembled properly once eligibility has been determined. Allocation concealment, a crucially important criterion, is protected if the person responsible for assigning a participant to an intervention is unaware of the randomisation code and is unable to manipulate the group allocation before or after assignation takes place (Mulrow & Oxman, 1997).

Performance bias is avoided through conducting a double-blind trial, which involves 'blinding' the patient and the clinician to the treatment received after randomisation occurs. In RCTs that compare drug therapies, this is accomplished by obtaining medications that are indistinguishable from one another (Hennekins, 1987). If the group assignment is unknown to all parties, it is less likely one group will be treated differently than the other.

The potential for attrition bias in a study could be determined if, in the published manuscript, the study author discussed the distribution of, and provided an explanation for, withdrawals and dropouts. Detection bias would be curtailed if the outcome

assessors were blinded to the treatment group and followed standardised measuring criteria.

All Cochrane reviews are required to include a quality score that rates the adequacy of allocation concealment. The criteria and four point scoring scale are as follows:

Criteria for concealment of allocation (Cochrane Handbook, 1996)

A = Adequate concealment
- Centralised or pharmacy-controlled randomisation
- Pre-numbered identical containers administered serially
- On-site computerised randomisation system unlocked after entering patients
- Sequentially numbered, sealed, opaque envelopes
- Other explicit schemes that seem to provide adequate concealment

B = Uncertainty about adequate concealment
- Merely stating list or table was used
- Merely stating sealed envelopes were used
- Information arousing suspicion of adequacy of concealment.

C = Inadequate concealment
- inadequate concealment approach e.g. alternation; days of the week
- transparent allocation procedure e.g. open list

D = not used as a criterion.

The use of an alternate scoring schema is optional. The scores can be used to establish a threshold for inclusion, or to explain variation in results (heterogeneity). They can also be used to weight each study in the final analysis or to perform sensitivity analyses (Mulrow & Oxman, 1996).

**v. Data collection**

Methodological and quantitative data are systematically collected from the studies onto standardised forms. When possible, the findings are converted into a common measure for statistical analysis. If conversions and calculations are required to achieve this goal, the methods must be recorded and verified. A protocol for checking data quality and correcting errors must be established.

**vi. Data analysis and interpretation of results**

Once the data have been abstracted, reviewers must decide which comparisons are appropriate, which study results to include in each comparison, and which summary measure is most appropriate. These decisions depend on the study question(s) and should follow the a priori comparisons outlined in the protocol when possible. In some instances, changes are necessary due to the nature of the available data. Measures of effect can be summarised using the odds ratio, the relative risk, or the mean difference. The 'mean difference' represents within study comparisons of outcome measures between the intervention group and the control group, or it represents a change in before and after measurements within each group.

In RevMan, (the computer software developed by the Collaboration for reporting a review) dichotomous variables are tabulated as the number of people who experienced the event in each comparison group and the total number in each group. Continuous variables are tabulated as the number of people in each group, the mean value for the outcome in each group and the standard deviation (SD) for each mean. At present, RevMan treats crossover trials as parallel group studies. In reviews where trials employing both designs are included, separate pooled estimates are calculated for crossover and parallel study data. RevMan has the capability to sort data according to effect size, weight, year, author, a unique user defined order, or by quality (the concealment allocation score).

Often, continuous outcome measures among the independent studies are tabulated on different scales but are thought to be comparable (for example, symptom scores using a scale of 1 to 10 vs. a scale of 1 to 35). When this is the case, it is possible to obtain the pooled estimate as a 'standardised mean difference' (SMD). However, for continuous outcomes that are measured in a uniform manner, a 'weighted mean difference' (WMD) is used, as it reports results in natural units that are easily understood.

The statistical methods used in meta-analyses calculate a weighted average of the results from the included trials such that those with narrower confidence intervals (generally the larger trials) have more influence (Egger, 1997). The weight used is the inverse of the variance for the estimated measure of effect (Mulrow & Oxman, 1997). The confidence interval (CI) around the pooled estimate indicates how precise that estimate is for a particular alpha level.

Two models for calculating the CIs are available in RevMan: the 'fixed effects' model and the 'random effects' model. The 'fixed effects' model assumes that an intervention has a true single effect. Therefore, differences between study results are due to random variation. The 'random effects' model assumes there is a different underlying effect for each trial and that that difference is randomly distributed. The random effects model incorporates this variation into the pooled result to guard against underestimating the standard error and is considered to be the more conservative of the models (Petitti, 1994). The fixed effects model generally produces narrower CIs in the face of heterogeneity and should not be used to compensate for this (ibid). Neither model is considered 'correct' and estimates in the pooled result, using either method, will not differ substantially unless there is significant heterogeneity (Petitti, 1994; Egger, 1997). RevMan, therefore, allows readers to move between the two results.

**vii. Interpretation of results**

The results from each comparison are displayed graphically in MetaView, a segment within RevMan (examples in Appendix H). The data are entered in such a way that results in the area to the left of the centre line indicate a beneficial effect is obtained from the intervention. The data can be examined in the following sequence:

1. Examine the confidence intervals among the study estimates. If they overlap with one another, the magnitude of the treatment effects obtained in the individual studies are relatively homogeneous. If they do not, this suggests that heterogeneity exists (Mulrow & Oxman, 1997).

2. Examine the Chi-square test of heterogeneity located in the bottom left hand corner of the graph. If the test value is statistically significant at the 5% or even perhaps the 10% level it suggests that the observed differences in individual study estimates are likely to be due to factors other than chance (Mulrow & Oxman, 1997).
3. When there is evidence of heterogeneity, sensitivity analysis based on study quality, sample size, publication status, etc. should be performed to examine the impact of selected review methods on the pooled estimate. Statistical significance aside, reviewers should consider whether the differences are clinically important based on what is known about the biology, psychology, or sociology of the topic being investigated. Reviewers need to report significant heterogeneity but are warned to be cautious in attributing between study differences to any one factor (Mulrow & Oxman, 1997).
4. If, a priori, the review sought to examine the effect of treatment subject to particular strata, then subgroup analysis can be carried out regardless of the extent of heterogeneity. If subgroup comparisons help to explain heterogeneity and there is a credible explanation, then the subgroup results should be presented. However, again Cochrane reviewers are advised to interpret subgroup analyses with caution since participants were randomised within individual studies, but not among the studies (ibid).

A systematic review that does not include a meta-analysis can be as valuable as one that does. It often does not make sense, and may even be misleading, to combine results from independent trials when two unrelated outcome measures are reported, even when these outcomes are related to a common objective. An example of this is combining pulmonary function changes with quality of life scores when both are being used to measure the effect of education interventions. It is equally unwise to pool results from studies that are only marginally relevant or are of poor quality. In these cases, it is helpful for decision makers to know that there are no reliable data available (ibid). The results of a review are intended to help clinicians and consumers make practical decisions about healthcare. Summations in a review, whether in words or in

numbers, need to be reliable and as free from bias as possible, therefore, if no conclusions can be drawn from the best available evidence, this knowledge can be used to stimulate appropriate follow-up research.

**viii. Peer review**

When the question for a new review is submitted to the appropriate Cochrane Review Group for consideration, an editor is assigned to the review team. The assigned editor must review the protocol, and later, the completed review, prior to sending it to the co-ordinating editor for that particular review group. Subject to the approval of both editors, the review is submitted for external evaluation.

## Section 2: Crossover trials

An important aspect of the appraisal of the studies included in the development and preparation of the meta-analysis on which this thesis was based, involve issues that pertain to a crossover design since all of the trials included employed this design.

### 2.2.1 Overview of the crossover design

Crossover designs in clinical trials have enjoyed popularity particularly in the areas of research into the safety and efficacy of new drugs (Jones & Lewis, 1995). A crossover trial is one in which individual participants are randomly allocated to different sequences of treatments (Senn, 1994). Every participant receives every treatment in the specified sequence order during equal length but separate time periods. The number of discrete interventions under study will determine the number of sequence patterns and periods. The effects of the different treatments on the same subject are compared for each period and the estimated treatment effect is the mean of the differences (Hills & Armitage, 1979).

The researchers need to ensure uniformity and balance within the sequences. Uniformity will ensure that each treatment appears in each sequence the same number

of times and each sequence appears the same number of times in each period. Balance, (sometimes referred to as counterbalancing), ensures that an equal number of subjects receive the treatments in reverse order (Woods, 1989). For example, in a two-treatment, two-period crossover, where treatment A and treatment B are being compared, the two sequences would be AB and BA. In a multi-period crossover, each treatment must follow every other treatment an equal number of times (e.g. ABC, CAB, BCA or CBA, ACB, BAC).

### 2.2.2 Appropriate use of the crossover design

Crossover designs are only appropriate when certain criteria are met:

1. The disease condition must be one that is chronic and stable, where the underlying severity will not change over the course of the study. This being the case, the goal of intervention is to alleviate or avoid symptoms in the short term rather, than to effect long term prophylaxis or cure (Hills & Armitage, 1979).
2. Not only must participants be stable and chronic, but they must revert quickly to the same pre-study baseline values when the treatment is stopped. If one of the treatments in period one leaves the patients in a relatively permanent but unequal state then by definition, participants cannot be crossed over to the next period (Kenward & Jones, 1987). Crossover designs are best suited to interventions that do not have a history of a long term action or of side effects.
3. The design is very suited to single dose testing when results can be assessed quickly. Examples include bioavailability or bioequivalent studies, assessment of immediate effect such as pain relief, or for immediate prophylaxis, as was the goal in the EIB trials.
4. Crossovers are the design of choice when the aim is to study patient-by-treatment interactions, because one can readily determine the proportions of subjects who respond or do not respond to an intervention, and at the same time assess patient preferences.

### 2.2.3 Advantages of the crossover design

The chief advantage of the crossover design lies in the fact that treatment comparisons are made on inter-patient rather than intra-patient differences. Inter-patient measurements are known to be more stable, with decreased variation and higher correlation, than between-patient measures (Kenward & Jones, 1987). With less variability, the estimate of treatment effect has better precision thus increasing statistical efficiency and power to detect a treatment effect of a given size. All this is accomplished with a smaller sample size than a parallel design would require to detect the same size of effect (Kenward & Jones, 1987). Therefore, in a meta-analysis, by ignoring the crossover design and analysing the data as though they were from a parallel study design, one is biasing the results towards the null.

### 2.2.4 Disadvantages of the crossover design

Achieving increased power with a smaller sample size benefits recruitment and financing in a study but it becomes a disadvantage if there are many dropouts or outliers. The data from dropouts cannot be analysed if they did not receive all of the interventions and outliers have the potential to carry more weight and cause considerable distortion of results (Altman, 1991).

The chief disadvantages of the crossover design lie in two potential biases related to time, a 'period effect', and sequence, a 'treatment-by-period interaction' (Altman, 1991). A period effect can occur if there is some difference between the periods of the trial that cause the results from the second period to be systematically higher, or lower, than results from the first period, independent of the treatments. This situation could arise if most patient's generally improved or deteriorated over the study periods such that the baseline values from period one to period two were not equal. A small period effect is not considered to be of serious concern when it applies to both treatments (Altman, 1991).

A treatment-by-period interaction (sequence effect) is considered to be the more serious of the disadvantages. In this situation, the treatment effect is influenced by the

order in which treatments were received due to a carry-over effect, positive or negative, from one of the treatments in the first period. If a sequence effect exists, then one sequence group will show a significantly different treatment effect when compared to the reverse sequence (Woods, 1989; Altman, 1991).

When there is an unequal carry-over of one the treatments in period one, it could be related to either pharmacokinetic or psychological factors. The possibility of pharmacological carry-over can be reduced by restricting the interventions to drugs that are known to have a short duration of action and that are rapidly cleared from the body (Shapiro, 1983). In addition, many trials include a 'washout' of adequate length, between treatment periods. The length of an adequate washout is considered to be a period of time equal to five to ten times the half-life of the drug (Lloyd & Raven, 1994). Psychological carry-over can be partially controlled through blinding subjects to the medications, the washout time, and the crossover time. Coupling qualitative with quantitative measures can also help to reduce the possibility of bias (Cleophas, 1990).

### 2.2.5 Analysis of crossover trials

Typically, in a crossover trial using baseline measurements, each subject provides two observations per period. The treatment effect is tested by performing a one sample t-test on the before / after differences within each patient (Altman, 1991). It is considered an unbiased estimate if there is no period effect or treatment-by-period interaction. When the possibility of either cannot be discounted, it is desirable to check for them in the analysis. Several techniques have been suggested in the literature but there appears to be no consensus. Grizzle, one of the first to address the problem in 1965, recommends a two step procedure that was outlined in detail in an article by Hills & Armitage (1979). The first step involves a test for a significant carry-over effect. In step two, the analyst proceeds dependent on the result obtained in step one. If the test result in step one indicates a non-significant carry-over, then the overall treatment effect is calculated using the full data set as described above.

However, if the result is statistically significant, the investigator then has two options. The first option is to discard all subsequent period data and analyse period one as though it were conducted as a parallel study. Statistical power to detect a difference is lost when this approach is taken. The second option is to estimate the magnitude of the carry-over effect and include it in the equation to estimate the treatment effect (Fleiss, 1989; Senn & Hildebrand, 1991).

# Chapter Three

## Section 1: Research objectives

### 3.1.1 Research objective

The purpose of this research was to provide health care professionals, patients, parents, coaches, trainers, and other end-users with a valid and current overview of the best scientific evidence available regarding the use of nedocromil sodium to treat exercise-induced bronchoconstriction in people with asthma. The objectives, which are outlined below, could best be accomplished by following the Cochrane Collaboration format for conducting a systematic review and meta-analysis which were discussed in Chapter 2. The use of this framework would enable the author to provide an unbiased summary estimate of the effectiveness and safety of using a single, prophylactic dose of NCS for EIB. (Refer to Appendix A for the protocol for the EIB review)

### 3.1.2 The research question

*Does the evidence from randomised, controlled, double-blind clinical trials support the use of a single prophylactic dose of nedocromil sodium (NCS) to prevent or attenuate exercise-induced bronchoconstriction (EIB) in people with asthma and reproducible EIB?*

### 3.1.3 Specific research objectives

1. To provide a pooled estimate of the effect of administering a single prophylactic dose of NCS on pulmonary function (FEV1 and / or PEFR) following a standard exercise challenge.
2. To determine if the dose of NCS, the delivery method, the timing of pre-treatment, the severity of EIB, the age, or the sex of the participants influenced the magnitude of effect.
3. To determine if prophylactic use of NCS influenced the time-course of EIB in the immediate post exercise period.
4. To determine other benefits or harms related to nedocromil sodium.

### 3.1.4 Inclusion Criteria (See Appendix B for working document)

**i. Study design**

Studies that were randomised, placebo-controlled, clinical trials were considered for inclusion.

**ii. Population of interest**

Studies in which the selected participants were diagnosed with asthma were considered for inclusion. They must have a history of, or objective evidence of EIB prior to inclusion in the trial. EIB was defined as a maximum percent fall in FEV1 or PEFR of 10 % or greater (described in 1.1.8). Children and adults would form subgroup analyses. Children must be 6 years or older; adults, 18 years or older.

**iii. Intervention of interest**

Studies in which participants were randomised to receive either nedocromil sodium or an inert placebo, administered as a single, prophylactic medication prior to a standardised exercise challenge of sufficient intensity and duration to trigger EIB were considered for inclusion.

**iv. Outcomes of interest: both objective and subjective would be considered**

1) An objective measure of the change in lung function comparing pre-exercise baseline values with post-exercise values e.g. FEV1 and PEFR
2) Other physical measures such as heart rate, respiratory rate
3) Adverse effects, disadvantages
4) Effect on physical performance
5) Effect on symptoms of EIB
6) Subjective satisfaction

## Section 2: Methods

### 3.2.1 Eligible studies

The search for eligible studies was conducted without regard to language or publication status. A priori, reviewers made the decision to exclude any data that were available only in the form of an abstract.

An electronic search of the ARG register was completed using the following search terms:

a) Asthma OR Wheez* AND

b) exercise* AND

c) Nedocromil* OR Tilade

d ) RCTs are identified using the terms: placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study in title, abstract or 'mesh-keywords'. This model was adapted from the Cochrane search strategy described in the Handbook (1997).

Two other data bases, the Cochrane Controlled Trials Register and Current Contents were also searched. To assure completeness, the reference lists of the included trials plus appropriate review articles and textbooks were examined by one of the reviewers.

The initial searches were scanned by one reviewer who excluded citations that were clearly irrelevant. The second screening was conducted by two reviewers using abstracts, titles and keywords, to independently identify trials that appeared potentially relevant. The text had to suggest that the trial was a clinical trial, and that it involved NCS and EIB (called by any of the alternative descriptors). If a trial looked potentially relevant, the reviewers requested the full text of the article be procured. The full text article was screened, by two reviewers, again independently, using the 'Criteria for Inclusion' (Appendix B). The reviewers were not blinded to the authors, journal of publication, or results of the studies as investigator bias was deemed

unlikely. Agreement using the kappa statistic was calculated for each level of screening. Disagreements were resolved by discussion and consensus.

An attempt was made to contact at least one author from each included trial to assess willingness to confirm data extraction, or to supply additional information about the primary research. Several pathways were pursued to locate the authors including letters to an address presented in the article (Appendix E), Internet 'people searches', electronic author searches in library databases for the address on the most recent article published by that author, and contact with other reviewers in the ARG.

A list of the studies selected for inclusion was sent to an author of each primary study and to the present manufacturer of NCS, Rhône-Poulenc Rorer. Each was asked to identify any additional relevant published, unpublished or 'in-progress' studies for the review.

### 3.2.2 Quality appraisal of included studies

Each trial was appraised by two reviewers using two different validity scales that are widely used in Cochrane Review Groups.

1) The Cochrane approach to assessment of allocation concealment, a 4 point scale described in 2.1.5.
2) A 5 point scale described and validated by Jadad (1996) and summarised as follows: (Appendix D)
   - Was the study described as randomised (1 = yes; 0 = no)
   - Was the study described as double-blind (1 = yes; 0 = no)
   - Was there a description of withdrawals and dropouts (1 = yes; 0 = no)
   - Was the method of randomisation well described and appropriate (1 = yes; 0 = no)
   - Was the method of double blinding well described and appropriate (1 = yes; 0 = no)
   - Deduct 1 point if methods for randomisation were inappropriate
   - Deduct 1 point if methods for blinding were inappropriate

Agreement was measured using the kappa statistic. Disagreements were resolved by discussion and consensus.

### 3.2.3 Data abstraction

Three forms were created and data were abstracted for three purposes.

First, information describing study characteristics was abstracted for the 'Table of Included Studies' found in RevMan, the software designed by the Collaboration to construct a review. The information was used to evaluate similarities and differences in methods, participants, interventions, and outcomes to support or reject the argument for statistically combining the data in a meta-analysis. The variables that were of interest are outlined in Table 3.1.

One reviewer used this template to enter data directly into RevMan. The 'Table of Included Studies' was printed and checked, by the same reviewer, against the original articles at least twice, to assure accuracy and completeness. (the Table is found in Appendix C)

**Table 3.1 Variables for 'Table of included studies'**

| | | | |
|---|---|---|---|
| **Citation** | 1. authors, title, journal, year published<br>2. concealment allocation score | | |
| **Method** | 3. study design<br>4. number of test days, frequency of testing<br>5. withdrawals and dropouts<br>6. concomitant therapy, how concomitant therapy handled<br>7. description of exercise challenge, environmental conditions | | |
| **Participants** | 8. country trial conducted in<br>9. recruitment procedure<br>10. age range (mean)<br>11. sex<br>12. inclusion/exclusion criteria<br>13. definition of EIB used for inclusion | | |
| **Interventions** | 14. drug treatments studied<br>15. dose of drug(s) studied<br>16. delivery system used<br>17. time of pre-treatment prior to exercise challenge | | |
| **Outcomes** | 18. instruments used to measure outcomes<br>19. PFT measures recorded and time of recording<br>20. calculations performed and outcome measures reported<br>21. adverse effects<br>22. statistical analysis | | |
| **Notes** | 23. Jadad score | 24. author contact | 25. other information |

The second form developed was used to abstract data that were later entered into the RevMan data tables. The variables are summarised in Table 3.2. Data were abstracted independently, by at least two, and in some cases three, independent reviewers. Each person involved was given instructions on the meaning of the variables and any conversions or calculations that might be required. Validity checks were conducted and the few discrepancies identified were resolved by reviewing the original article and coming to a consensus. Data were entered into the appropriate comparison groups in the data tables in RevMan 3.01. Two people conducted validity checks on all tables.

**Table 3.2 Variables for analysis***

| | | | | | |
|---|---|---|---|---|---|
| study # | first author | date published | country | Def'n EIB used | Tx's given |
| doses studied | delivery method | time pre-tx | sample size | age range | adult/child |
| # male | # female | PFTs recorded | control: mean max % fall FEV1 | SD of ← | placebo: mean max % fall FEV1 |
| SD placebo FEV1 | NCS: mean max % fall FEV1 by dose | SD NCS FEV1 by dose | control: mean max % fall PEFR | SD of ← | placebo mean max % fall PEFR |
| SD placebo PEFR | NCS mean max % fall PEFR by dose | SD of ← | placebo: mean max % fall FEV1 @ 135 min | SD of ← | NCS: mean max % fall FEV1 @ 135 min |
| SD NCS FEV1 @ 135 min | placebo: mean max % fall FEV1 @ 255 min | SD of ← | NCS: mean max % fall FEV1 @ 255 min | SD of ← | |

*read left to right

The third form, Table 3.3, was designed to record data taken from graphs that had been included in thirteen of the manuscripts. These graphs depicted the time-course of EIB following the exercise challenge. The mean % fall in FEV1 for both NCS and placebo were plotted for time points 0 to 1, 3, 5, 10, 15, 20 and 30 minutes post-exercise. Since the actual value of the mean % fall FEV1 plotted at these time points was not reported, the reviewers chose to enlarge the graphs and draw grid lines. Two people independently estimated the values at each of the designated time points. Where there were differences in estimates, the mean of the two estimates was entered.

**Table 3.3 Mean % fall FEV1 at time-points post exercise***

| study # | adult/child | 0-1 min | 3 min | 5 min | 10 min | 15 min | 20 min | 30 min |
|---|---|---|---|---|---|---|---|---|
| Mean FEV1 | | | | | | | | |
| SD | | | | | | | | |
| 95% CI | | | | | | | | |

*There was a separate chart for NCS and placebo

Authors of primary studies who agreed to assist, were sent the data extracted from his or her article(s) and asked to confirm the data and the summary statistics. In some cases they were asked to supply missing data and information on trial design (Appendix F).

### 3.2.4 Data Analysis

**i. Data preparation**

1) A kappa coefficient of agreement between reviewers was calculated for the 'inclusion' ratings and for the 'validity' scores.

2) When only the standard error of the mean (SEM) was reported, the standard deviation (SD) was calculated using the formula:
SD = SEM x $\sqrt{n}$. Where 'n' represents the study sample size.

3) When only a pooled SD of the mean difference between treatments was reported, two options were used:
A SD for each treatment group was calculated from the individual patient data if it was provided in the publication.
The pooled SD, described below, was imputed. (Follman 1992).

The pooled SD* was calculated using the following formula:

$$\text{Pooled SD} = \sqrt{(n_1-1)var_1 + (n_2-1)var_2 + \ldots (n_k-1)var_k / \sum n - k}$$

Where var = the variance of the study group in study i, k = the number of studies with the variance provided.

*A separate estimate was calculated for adults and children, for FEV1 and for PEFR studies.

4) When no measure of variance was reported the pooled SD calculated as described was imputed.

Sensitivity analysis was performed on the effect of using imputed data.

**ii. Data Analysis**

The data were entered into RevMan 'Data Tables'. The data entered included the mean maximum % fall FEV1 (max % fall) (or the mean maximum % fall PEFR) on NCS and the respective SD, compared to the mean max % fall FEV1 (or the mean max % fall PEFR) on placebo and the respective SD. These measures are referred to as *expt* mean and *ctrl* mean respectively on the RevMan graphs in MetaView (Appendix G).

Results from similar studies were pooled and estimates of treatment effect were reported as the weighted mean difference (WMD) using the random effects model.

The analyses detailed below were completed. The comparison order follows the same order as the research objectives listed in 3.1.3.

**Objective 1**

Data were pooled for the following comparison groups:

1. Maximum % fall FEV1
   i. any dose NCS / any delivery system
   ii. placebo
2. Maximum % fall PEFR
   i. any dose NCS / any delivery system
   ii. placebo

**Objective 2**

Subgroup analyses were performed for the following:

1. NCS vs. placebo based on age group (cut point <18 / ≥ 18 years)
   a) mean max % fall FEV1
      i. children
      ii. adults

b) mean max % fall PEFR
   i. children
   ii. adults

2. NCS vs. placebo based on dose of NCS
   a) mean max % fall FEV1
      i. ≤ 2 mg NCS
      ii. 4 mg NCS
      iii. ≥ 6 mg NCS
   b) mean max % fall PEFR
      i. ≤ 2 mg NCS
      ii. 4 mg NCS
      iii. ≥ 6 mg NCS

3. NCS vs. placebo based on delivery system
   a) mean max % fall FEV1
      i. 4 mg NCS using MDI with spacer
      ii. 4 mg NCS using MDI alone
   b) PEFR data not available

4. NCS vs. placebo based on time of pre-delivery
   a) mean max % fall FEV1
      i. < 30 minutes pre-exercise
      ii. ≥ 30 minutes pre-exercise
   b) mean max % fall PEFR
      i. < 30 minutes pre-exercise
      ii. ≥ 30 minutes pre-exercise

5. NCS vs. placebo based on severity of EIB
   a) mean max % fall FEV1
      i. mean max % fall FEV1 < 30% on placebo
      ii. mean max % fall FEV1 ≥ 30% on placebo
   b) mean max % fall PEFR
      i. mean max % fall PEFR < 30% on placebo
      ii. mean max % fall PEFR ≥ 30% on placebo

A subgroup comparison based on sex of participant could not be completed because of insufficient data.

**Objective 3**

Data estimated from graphs, (described in 3.2.3) were entered into Excel (Microsoft® Office for Windows 95). The mean and SD of the % fall FEV1 for each time point was calculated for the NCS and placebo challenges. The Mann Whitney U procedure was used to test for a significant difference at each time point.

**Objective 4**

1) Data for two additional pulmonary function indices, the forced vital capacity (FVC), and the forced expiratory flow rate through the middle portion of the vital capacity ($FEF_{25-75}$), were reported in some studies. These data were entered and analysed in RevMan.
2) Data evaluating the duration of effect of NCS vs. placebo in subsequent exercise challenges on the same study day were reported in three studies. These data were entered and analysed in RevMan.
3) Data for other benefits attributable to NCS were not reported.
4) Data for adverse effects were not collected and reported systematically in any trial.

# Chapter four

## Section 1: Results from the literature search

### 4.1.1 Identification of eligible studies

More than 2000 titles, abstracts, and citations, from all data sources, were scanned by one reviewer to assess them for potential relevance to the research question and objectives. Eighty-six titles and abstracts were selected from the computerised databases. Forty-seven of the eighty-six citations were discrete studies (due to duplication in the databases). Four additional citations were identified from the reference lists of relevant publications for a total of fifty-one potentially relevant studies. From the text in title, abstract, and keywords, two reviewers independently selected 32 of the 51 (63%) for full text review [kappa 0.92]. Two reviewers determined that twenty-two trials met the inclusion criteria [kappa 0.75]. Further discussion and clarification of the inclusion criteria resulted in 100% agreement for the inclusion of the twenty-two trials.

Four of the 51 trials identified were foreign language studies, two were published in German, one in Spanish and one in Italian. Each of these studies was independently screened by colleagues familiar with the respective languages and the inclusion criteria. All of the studies were excluded: two were not randomised (Magnussen, 1986; Morandi, 1982), one did not report compatible outcomes (Bauer, 1988), and one study compared NCS to another active drug rather than an inert placebo (Hoffmeister, 1995). Three of the 51 citations identified were published as abstracts only (Bleeker, 1995; Patel, 1987; Mihalyka, 1988). The authors of the abstracts were contacted, however, full manuscripts could not be provided for two of the three. A third author did offer an unpublished manuscript (Mihalyka, 1988). The study met the inclusion criteria and was included.

Among the 51 trials that were considered for inclusion, there were two sets of duplicate publications, Shaw and Kay (1985), and Thomson and Roberts (1985). Data from these publications were included only once.

In the group of 22 trials selected for inclusion[2], there were three trials published by de Benedictis and colleagues; and three others published by Boner and associates. All of these studies were conducted in the same country. A reviewer was able to contact these authors to confirm that none of the subjects participated in more than one of these investigations. The six studies were therefore included as independent trials.

### 4.1.2 Quality Appraisal

1) There were two trials where the 'concealment of allocation' assessment was rated as 'A' or clear (N = 2)[3], the remaining studies rated 'B' or unclear (N = 19). [simple agreement 90%, kappa 0.88]. Disagreements were discussed and consensus reached. (Refer to 2.1.5.iv)
2) Quality scores were also determined for each study using the Jadad validity scale (refer to 3.2.2.ii). This 5 point scale ranges from 3 to 5, with higher scores implying better study quality. All studies in this review were rated with 'good' to 'high' quality ratings [simple agreement 81%, kappa 0.67]. Disagreements were discussed and consensus reached. In the final analysis, there were two trials that rated '5', nine trials that rated '4', and ten trials that rated '3'. According to the five criteria, all authors reported that trials were both randomised and double-blind and all studies described withdrawals and dropouts[4], or the data indicated there were none; therefore, all studies received a minimum score of three. In the majority of manuscripts, there was often missing information with regards to the other two criteria, the methods used to randomise, and the methods applied to ensure double-blinding.

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[2] There were 15 primary authors for the 22 studies included in the review

[3] N refers to the number of studies

[4] There were 12 withdrawals because they could not demonstrate reproducible EIB. There was one dropout due to an exacerbation of asthma following the placebo run. The person was too ill to complete the protocol and is not included in the analysis.

### 4.1.3 Crossover design in the EIB trials

All of the trials that met the inclusion criteria for the meta-analysis on which this thesis is based, used crossover designs. This design was an appropriate choice for studying the acute effect of nedocromil on the EIB response (refer to 2.2.2). The participants in these studies had chronic asthma but no other complicating medical condition. During the study period, each participant was considered to have stable lung function. This meant the pre study airflow values were ≥ 70% of the predicted values for individual height, weight, sex, and race. Also the variation in pre-treatment baseline values did not vary more than 10 to 15% from challenge to challenge. In all but one participant (who was made to drop out of the study), lung function returned to normal baseline values after the EIB response.

One of 280 participants, in all of the trials, was on a low dose of chronic oral steroids. The remaining 279 people, however, were taking other standard maintenance asthma therapies ranging from $\beta_2$ agonists as needed, to daily inhaled anti-inflammatory prevention. In all of the studies, medications were discontinued prior to each exercise challenge to effect a washout period, however, carry-over effects due to concurrent therapy cannot be ruled out. It is reasonable to assume that any potential pharmacologic carry-over would be randomly distributed over the individual study groups as well as the independent trials. If present, a carry-over effect would most likely bias the treatment effect towards the null, since anti-asthma therapy would tend to decrease bronchial hyperreactivity and thereby, attenuate the EIB response.

Seven of the trials in the review studied one other drug in addition to NCS and a placebo. No pharmacologic carry-over effects attributable to the study drugs were likely in any trial since the half-life of each drug studied was short. Of the drugs studied; nedocromil has a half-life of 1.5 to 2.0 hours, sodium cromoglycate a half-life of 80 minutes, furosemide a half-life of 2 hours (CPS, 1997). All of these drugs would be virtually cleared from the body within 24 hours. Though there was variation among individual trials, all had at least 24 hours between exercise challenges, most had longer

(Table of Included Studies, Appendix C). Twenty-four hours between challenges would comply with the suggestion that there be a period of time equal to 5 or 10 times the half-life between study periods. These trials involved a single dose of study medication administered once prior to an exercise challenge. There was no opportunity for an additive effect due to repeated dosing.

### 4.1.4 Contact with authors

Nine of the 15 (60%) primary authors were located and successfully contacted. Five were not able to confirm data abstraction nor provide additional information because the original study was not accessible. One the authors was able to provide the original trial data, three others confirmed data extraction but could not provide additional data.

When data extraction was completed, one additional study (Bauer, 1986) was dropped from the review. This study reported pulmonary function results using a specific airways resistance measure (sGaw), a value that cannot be converted nor combined with either the FEV1 or PEFR data. One other study, Sinclair (1990), did not report the maximum percent fall values and thus could not be included in that analysis, however, the study did report the time-course for the mean % fall FEV1 post exercise and the data were employed in that comparison.

## Section 2: Quantitative results

### 4.2.1 Study characteristics

The study characteristics are outlined in detail in the 'Table of Included Studies', and a summary table of study characteristics found in Appendix C. Collectively, data from twenty studies accounting for 280 participants are included in the various comparisons within the meta-analysis. The number of studies (N), the age, sex and sample size (n) distributions are itemised in Table 4.1 and Table 4.2. They are categorised by the primary outcome(s) reported in the studies. T hree studies reported only PEFR outcomes, five studies reported both FEV1 and PEFR outcomes, twelve studies reported only FEV1 outcomes. The Airways Group does not recommend combining

FEV1 and PEFR data in a meta-analysis using a standardised mean difference (SMD). For this reason, analyses for these outcomes remain separate.

**Table 4.1 Age, sex and sample size distributions of FEV1 studies**

| PFT reported | Total Studies | Children 6.5-17 yr | Adult 18-54 yr | Sample size | Children 6.5-17 yr | Adult 18-54 yr |
|---|---|---|---|---|---|---|
| Maximum % fall FEV1 | N=17 | N=11 | N=6 | n=240<br>m=164 (68%)<br>f=76 (32%) | n=162<br>m=111 (67%)<br>f=51 (31%) | n=78<br>m=53 (68%)<br>f=25 (32%) |

**Table 4.2 Age, sex and sample size distributions of PEFR studies**

| PFT reported | Total Studies | Children 6.5-17 yr | Adult 18-54 yr | Sample size | Children 6.5-17 yr | Adult 18-54 yr |
|---|---|---|---|---|---|---|
| Maximum % fall PEFR | N=7 | N=4 | N=3 | n=115 | n=75<br>m=54 (72%)<br>f=21 (28%) | n=40<br>m* =15<br>f* =11 |

* one study did not report sex distribution

### 4.2.2 Overall results

Nineteen trials reported the response to treatment using the maximum percent fall index described in section 1.1.10. The reader will recall that this index is a comparison of the maximum change in airflow obstruction before and after exercise. The two main outcomes were reported as the maximum % fall in FEV1 and the maximum % fall in PEFR. Figures 4.1 and 4.2 show the distributions of the mean maximum percent changes in pulmonary function before and after the control, the placebo, and the NCS challenge periods for the individual studies.

No study reported a significant change in lung function pre and post inhalation of either placebo or NCS in advance of the exercise challenge. This observation indicates that neither of these treatments had a bronchodilating effect prior to exertion.

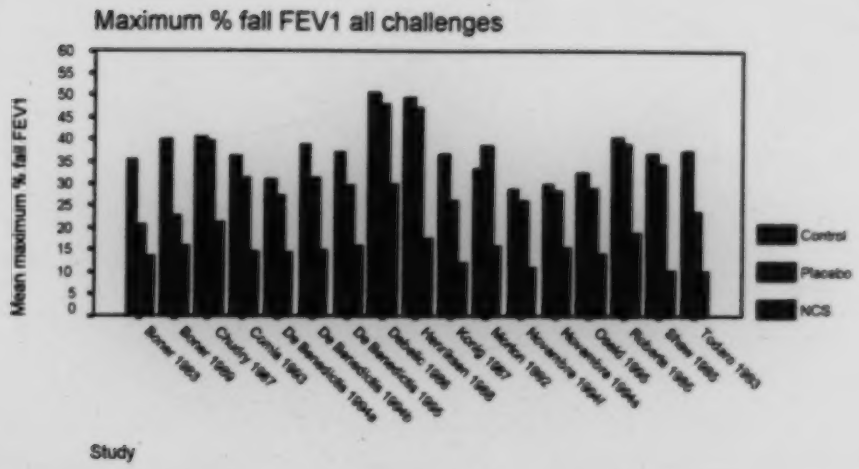


**Figure 4.1 Maximum percent changes in FEV1 in individual studies**

Fourteen of the seventeen (82%) FEV1 trials showed a statistically significant difference between NCS and placebo in favour of NCS.

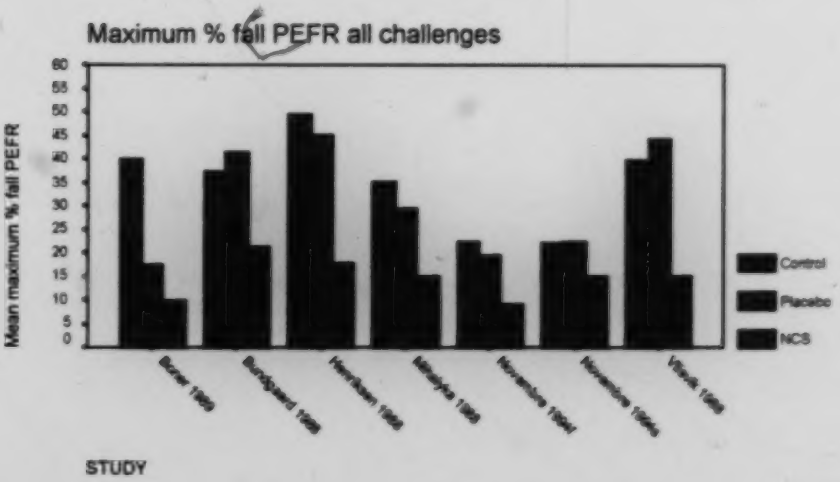


**Figure 4.2 Maximum percent changes in PEFR in individual studies**

Five of the seven (71%) PEFR trials showed a statistically significant difference between NCS and placebo in favour of NCS.

The outcomes in all trials were reported in identical units and originated from populations and interventions that were similar in nature. Consequently, we felt it was acceptable to combine the results for a quantitative pooled estimate of treatment effect. Figures 4.3 and 4.4 present the cumulative picture when the data are combined across all trials.

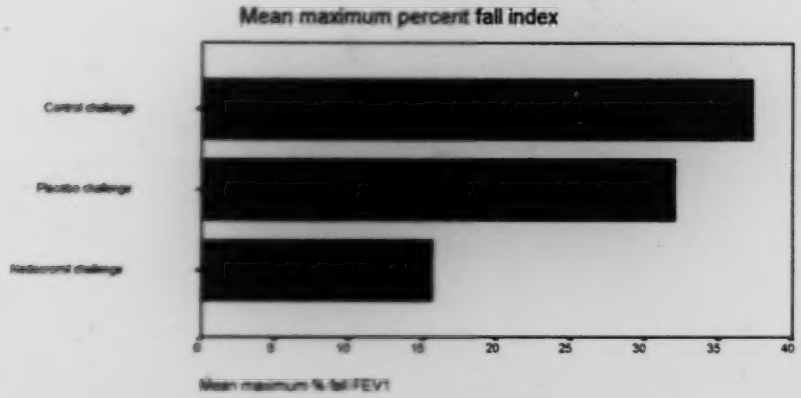


**Figure 4.3 Mean maximum % fall FEV1: all trials**

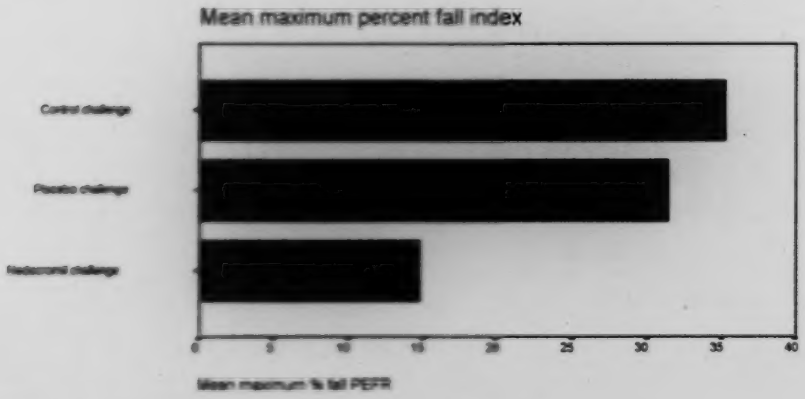


**Figure 4.4 Mean maximum % fall PEFR: all trials**

### 4.2.3 Objective 1: Combined result for all NCS treatment options

**1. FEV1 trials**

A pooled estimate of the weighted mean difference (WMD) in the mean maximum % fall in FEV1 after NCS and after placebo was calculated for the seventeen FEV1 trials. The results were combined regardless of dose or delivery options. If a trial studied more than one dose of NCS, the results for the 4 mg challenge were used. The variations in study characteristics included in this comparison are described in table 4.3. Figure 4.5 is a MetaView representation of the WMD in the individual studies and of the pooled estimate of treatment effect.

**Table 4.3 Characteristics of FEV1 studies in the pooled analysis**

| | | | |
|---|---|---|---|
| **Age group** | N=11 children, | N=6 adult | |
| **Dose of NCS** | N=1: 2mg | N=15: 4mg | N=1: 8mg |
| **Device** | N=5: MDI with spacer | N=12: MDI | |
| **Severity** | N=9: <30% | N=8: ≥ 30% | |
| **Timing** | N=10: < 30 min. | N=7: ≥ 30 min. | |

The WMD and 95% CI for this comparison was -15.64% [-13.15, -18.14%]. No significant heterogeneity was found in this result ($\chi^2$ 17.6; df=16, NS[5]). This result suggests that when NCS was used, the maximum EIB response was significantly attenuated by an estimated 16%. This magnitude of improvement is also thought to be clinically significant (ATS, 1993, CCG, 1996).

[5] NS represents a non statistically significant result at $\alpha = 0.05$

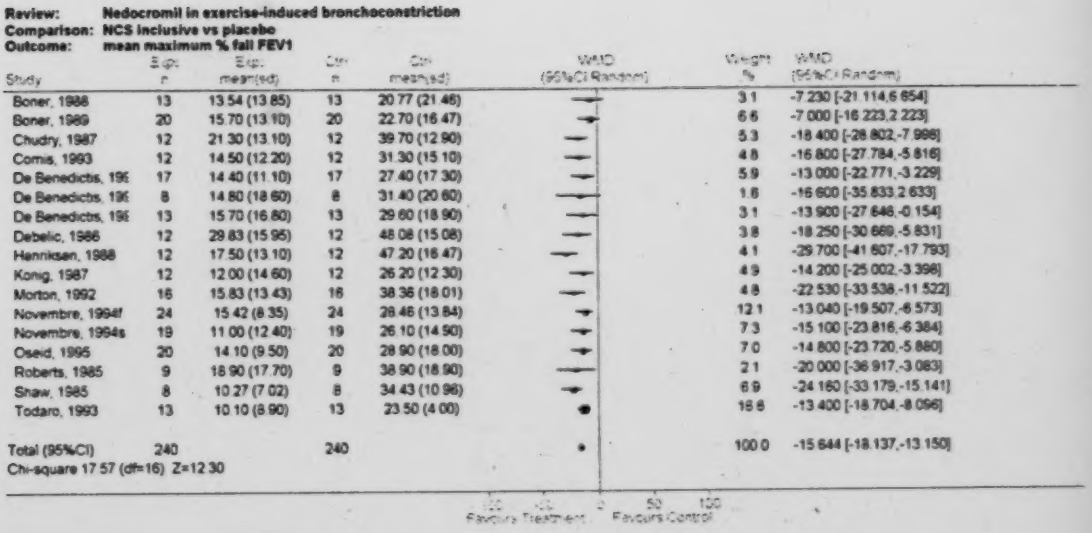


**Figure 4.5 Pooled result of all FEV1 trials**

## 2. PEFR trials

A pooled estimate of the weighted mean difference (WMD) in the mean maximum % fall in PEFR after NCS and after placebo was calculated for the seven PEFR trials. Again, the results were combined regardless of dose or delivery options and each trial was included only once. The variations in study characteristics included in this comparison are described in table 4.4.

**Table 4.4 Characteristics of PEFR studies in pooled analysis**

| | | | |
|---|---|---|---|
| **Age group** | N=4 children, | N=3 adult | |
| **Dose of NCS** | N=0: ≤ 2mg | N=7: 4mg | N=0: 8mg |
| **Device** | N=3: MDI with spacer | N=4: MDI | |
| **Severity** | N=4: <30% | N=3: ≥ 30% | |
| **Timing** | N=3: < 30 min. | N=4: ≥ 30 min. | |

The aggregate WMD and associated 95% CI for these studies was -14.98% [-8.34, -21.62%], an estimate that is similar to the FEV1 result in magnitude, however, there is more variability as evidenced by wider CIs. The test for heterogeneity was statistically significant ($\chi^2$ 20.28; df=6, p< 0.001. (Figure 4.6). The heterogeneity was considered in the sensitivity and subgroup analyses.

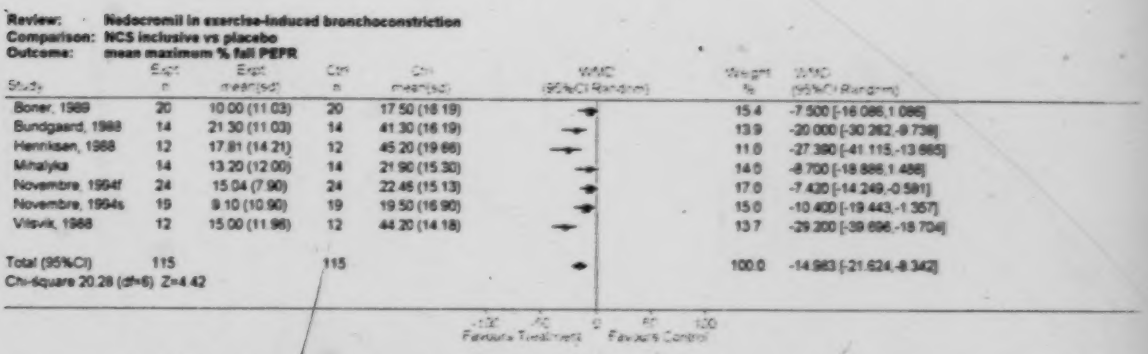


**Figure 4.6 Pooled result of all PEFR trials**

### The protection index

The protection index is another measure commonly employed and reported in the EIB literature. It is a measure of the clinical effect of a drug treatment in EIB. Inhibition of the drop in the FEV1 or PEFR by the active drug of 50% or more, over placebo therapy, is believed to represent a clinically significant difference (Anderson, 1995). Using these aggregate results, NCS provided a measure of 51% [95% CI: 46, 55%] protection against a decrease in FEV1 over a placebo. The level of protection provided ranged between 31 and 70%. In the PEFR studies the protection index was 49% [95% CI: 40, 58%], the range here was between 33 and 66%.

### Sensitivity analyses

Heterogeneity may be the result of differences in the populations, interventions and outcomes of the studies included in a meta-analysis. Alternatively, the heterogeneity may be the result of chance. Decisions regarding the methods to be used in a review

can also contribute to heterogeneity, and have the potential to contribute to a biased estimation of the effect of NCS. Therefore, sensitivity analyses were performed on the following decisions reviewers made regarding selection, inclusion, and analysis of data: the impact of imputing data, the impact of including unpublished data, the impact of study quality (using Jadad scores) and the impact of using the random vs. the fixed effects model.

**i. The impact of imputing a pooled SD: Table 4.5**

A pooled SD was imputed in the case of two studies in each of the FEV1 (Boner, 1989; Henriksen, 1988) and PEFR (Boner, 1989; Bundgaard, 1988) comparisons.

**Table 4.5 Sensitivity analysis: imputed data**

| | Effect on pooled WMD [95% CI] | |
|---|---|---|
| **PFT** | **Imputed** | **Not imputed** |
| **FEV1** | -15.64% [-13.15, -18.14%] | -15.51% [-13.06, -17.97%] |
| **PEFR** | -14.98% [-8.34, -21.62%] | -15.83% [-6.93, -24.73%] |

No significant impact on the estimated WMD was noted for either the FEV1 or PEFR outcome. The test for heterogeneity in the FEV1 studies was non-significant, and in the PEFR studies heterogeneity was significant ($\chi^2$ 16.88; df 4, $p < 0.001$). Given these findings, the remainder of the comparisons include studies with imputed data.

**ii. The impact of unpublished data**

The full manuscript from one PEFR trial (Mihalyka, 1988), was obtained from the author, however, it has been published in abstract form only. The impact of including this data was calculated. When the single study was removed, the WMD increased to -16.11% [95% CI: -8.50, -23.73%]. Compared with the imputed result listed in table 4.5, this is a non-significant change. This sensitivity analysis did not alter the test for heterogeneity ($\chi^2$ 19.4; df 5, $p < 0.01$). Given this finding, the study was retained in future comparisons.

**iii. The impact of study quality**

No significant impact on the weighted mean difference, for either the FEV1 or PEFR outcome, was noted when sensitivity analysis was performed based on study quality assessed using Jadad validity scores. (Table 4.6) We compared studies with lower scores, i.e. 3 or less, to those with higher scores, i.e. 4 or 5.

**Table 4.6 Sensitivity analysis: study quality**

| | Effect on pooled WMD [95% CI] | |
|---|---|---|
| **PFT** | **Jadad score ≤ 3** | **Jadad score ≥ 4** |
| **FEV1** | -14.16% [-11.21, -17.12%] | -17.90% [-12.33, -23.47%] |
| **PEFR** | -8.55% [-3.74, -13.35%] | -20.47% [-9.91, -31.03%] |

In the PEFR studies, the test for heterogeneity among the better quality studies remained significant ($\chi^2$ 11.98; df 3, $p < 0.001$). Given these findings, studies with Jadad scores of 3 were retained. (Appendix G, Figures 4.21 and 4.22)

**iv. Comparison of random effects model and fixed effects model**

The model used for analysis had a non-significant impact on the estimated WMD and 95% CI for either of the outcomes and the tests for heterogeneity were unaffected by the method of analysis (Table 4.7).

**Table 4.7 Sensitivity analysis: statistical model**

| | Effect on pooled WMD [95% CI] | |
|---|---|---|
| **PFT** | **Random effects model** | **Fixed effects model** |
| **FEV1** | -15.64% [-13.15, -18.14%] | -15.51% [-13.18, -17.84%] |
| **PEFR** | -14.98% [-8.34, -21.62%] | -13.28% [-9.76, -16.80%] |

This meta-analysis reports results using the random effects model because the model incorporates the variability between studies and is considered to result in a more conservative estimate of effect.

### 4.2.4 Objective 2: Subgroup analyses

Results from subgroup analyses are summarised in Table 4.8.

The MetaView graphs for these comparisons are found in Appendix G

**Table 4.8 Subgroup Analyses: Random effects model**

| | FEV1 data | | PEFR data | | |
|---|---|---|---|---|---|
| **SUBGROUP comparisons** | **$\chi^2$ (df) $\alpha$ 0.05** | **Max % fall FEV1 WMD [95% CI]** | **$\chi^2$ (df) $\alpha$ 0.05** | **Max % fall PEFR WMD [95% CI]** | **Appendix G** |
| **1. AGE** | | | | | |
| **children (6 to 17 yr.)** | 11.25 (10) NS | -14.81 [-11.45, -18.16] | 7.04 (3) $p < 0.10$ | -11.48 [-4.49, -18.48] | FEV1 Figure 4.7 |
| **adult (18 to 54 yr.)** | 5.71 (5) NS | -16.89 [-12.97, -20.81] | 7.59 (2) $p < 0.01$ | -19.25 [-7.65, -30.85] | PEFR Figure 4.8 |
| **2. DOSE** | | | | | |
| **≤ 2 mg NCS N=2** | 0.01 (1) NS | -24.37 [-16.54, -32.2] | 0.37 (1) NS | -13.36 [-5.46, -21.27] | FEV1 Figure 4.9 |
| **4mg NCS N=15(FEV1) N=7 (PEFR)** | 11.85 (14) NS | -14.51 [-12.04, -16.98] | 20.28 (6) $p > 0.001$ | -14.98 [-8.34, -21.62] | PEFR Figure 4.10 |
| **≥ 6mg NCS N=1** | N=1 | -22.53 [-11.52, -33.54] | N=1 | -21.80 [-9.01, -34.59] | |
| **3. DELIVERY** | | | | | |
| **MDI with Spacer 4mg NCS** | 1.82 (4) NS | -13.89 [-9.76, -18.02] | 0.27 (2) NS | -8.44 [-3.53, -13.35] | FEV1 Figure 4.11 |
| **MDI 4mg NCS** | 11.57 (11) NS | -14.75 [-11.79, -17.71] | 8.77 (3) $p < 0.05$ | -20.96 [-11.52, -30.41] | PEFR Figure 4.12 |
| **4. TIME** | | | | | |
| **< 30 minutes** | 7.85 (9) NS | -15.05 [-12.22, -17.87] | 0.27 (2) NS | -8.55 [-3.74, -13.35] | FEV1 Figure 4.13 |
| **≥ 30 minutes** | 9.31 (6) NS | -17.03 [-11.80, -22.26] | 11.98 (3) $p < 0.01$ | -20.47 [-9.91, -31.03] | PEFR Figure 4.14 |
| **5. SEVERITY** | | | | | |
| **< 30% fall** | 2.74 (8) NS | -12.84 [-10.03, -15.65] | 0.31 (2) NS | -8.30 [-4.10, -12.49] | FEV1 Figure 4.15 |
| **≥ 30% fall** | 3.77 (7) NS | -21.36 [-17.20, -25.52] | 1.64 (2) NS | -25.14 [-18.67, -31.14] | PEFR Figure 4.16 |

In summary, the data demonstrate a lack of significant difference in the estimated effect of NCS in subgroup analyses based on age, dose of NCS, delivery system, and time of delivery. The $\chi^2$ test for heterogeneity remained non-significant in the FEV1 comparisons, and statistically significant throughout the pooled PEFR results.

When the studies were dichotomised into groups based on the degree of EIB severity, the estimated effect of NCS was significantly different between the two for both outcomes. There was no heterogeneity in these results. This subgroup analysis indicated that NCS inhibited the reduction in lung function to a significantly greater degree in those with moderate to severe EIB. The differences in the magnitude of these responses are illustrated in Figures 4.17 and 4.18.

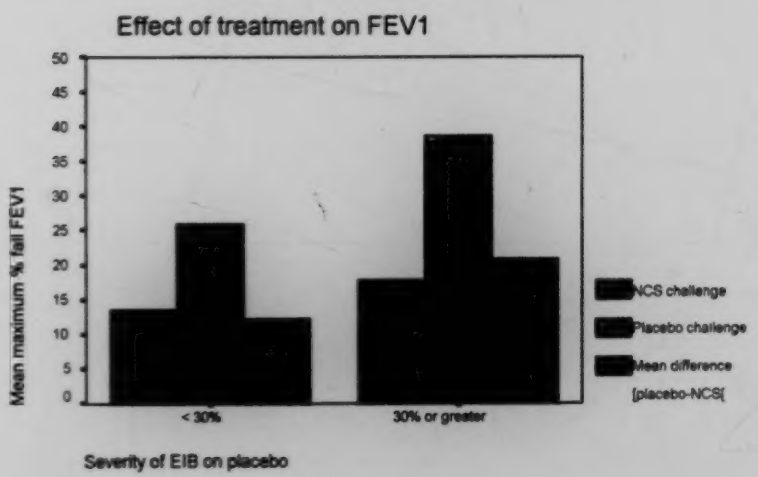


**Figure 4.17 Effect of treatment on mean maximum % fall FEV1**

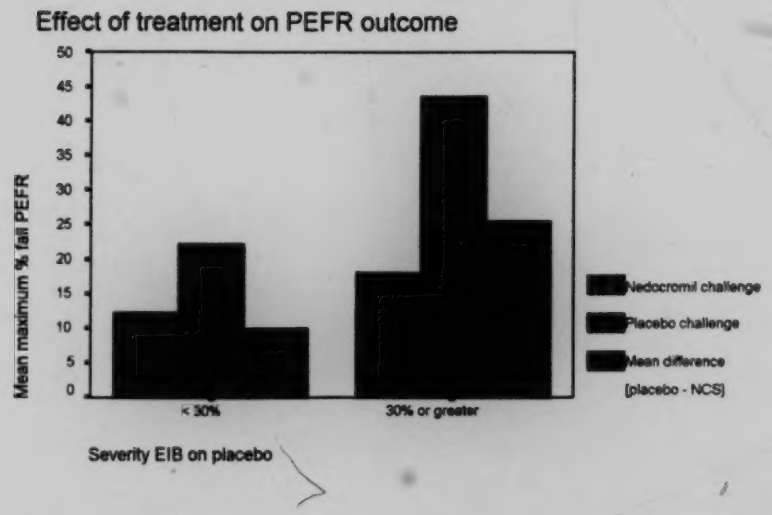


**Figure 4.18 Effect of treatment on mean maximum % fall PEFR**

### 4.2.5 Objective 3: Time course analysis

Thirteen studies reported data on the time-course of EIB after pre-treatment with NCS or placebo. Table 4-8 contains the data abstracted using the method described in section 3.2.3. These data are represented graphically in Fig 4.19. In summary, there was significant improvement in lung function in favour of NCS at every point measured. This improvement was clinically relevant between two and twenty minutes post challenge when EIB is typically at it's peak. Figure 4.19 also shows that following a single inhalation of NCS, recovery to normal lung function happened more quickly. The mean % change in FEV1 was within normal limits (i.e. < 10% change from baseline) in under ten minutes compared to more than 30 minutes following placebo.

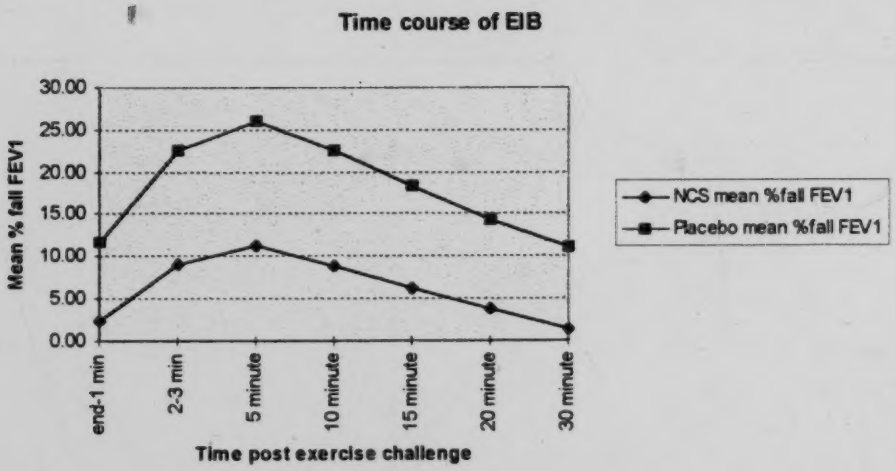


**Figure 4.19: Treatment effects on the time-course of EIB**

**Table 4.9 Time-course analysis**

| TIME | Mean % fall FEV1 | | Mean % fall FEV1 | | Mean difference NCS - placebo 95% CI | Mann-Whitney test |
|---|---|---|---|---|---|---|
| | NCS | SD | Placebo | SD | | α 0.05 |
| 0-1 min N=13 | 2.47 | 5.04 | 11.74 | 7.97 | -9.27 [-3.87, -14.67] | p=0.001 |
| 2-3 min N=13 | 9.11 | 6.97 | 22.46 | 6.45 | -13.35 [-5.58, -21.12] | p=0.002 |
| 5 min N=13 | 11.28 | 5.10 | 26.04 | 6.40 | -14.76 [-9.10, -20.41] | p=0.000 |
| 10 min N=13 | 8.80 | 4.04 | 22.64 | 6.33 | -13.84 [-9.49, -18.20] | p=0.000 |
| 15 min N=12 | 6.29 | 3.46 | 18.42 | 5.59 | -12.13 [-7.77, -16.45] | p=0.000 |
| 20 min N=10 | 3.75 | 2.88 | 14.34 | 11.65 | -10.62 [-6.44, -15.85] | p=0.000 |
| 30 min N=5 | 1.43 | 1.38 | 11.13 | 8.46 | -9.70 [-3.77, -15.63] | p=0.008 |

These data were approximated from graphs published in the original articles. It would have been preferable to have discrete patient data, but this information was not available from the authors.

The a priori sub-group comparison to examine gender differences was abandoned due to incomplete reporting. No examination of the effect of current asthma therapy could be undertaken for similar reasons.

### 4.2.6 Objective 4: other benefits or harms related to NCS

A priori, the reviewers intended to examine all reported outcomes, whether they were physiological or subjective in nature. In addition to the two measures already described, data were provided on two other measures of pulmonary function, the forced vital capacity (FVC), and the forced expiratory flow in the mid-portion of the FVC abbreviated as FEF25-75. These measures are sometimes recorded when assessing EIB in athletes because a reduction in these flow rates, particularly the FEF25-75 can reduce maximum exercise performance (Anderson, 1995).

**i. Other pulmonary function data**

Three studies reported the change in the FVC. The pooled MWD was -9.00 [95% CI: -1.67, -16.32%]. A decrease of 20% in this measure is considered to have clinical significance (Virant, 1992). (Appendix G, Figure 4.17)

Five studies reported the change in the FEF 25-75 pre and post exercise challenge. The pooled MWD was -16.47% [95% CI: -10.05, -22.88%]. A 20% decrease would be considered clinically relevant (Virant, 1992). (Appendix G, Figure 4.18)

**ii. Duration of effect**

Three of the trials (Konig, 1987; de Benedictis, 1995; Chudry, 1987;) were designed to study the duration of the effect of a single dose of nedocromil. In these studies, the participants engaged in two or three exercise challenge tests on the same day. Prophylactic treatment was offered prior to the first challenge only.

All three studies reported data on the change in FEV1 following a second exercise challenge that was undertaken either 120, 140, or 150 minutes, respectively, after pre-treatment. The pooled MWD for these challenges was -5.95 [95% CI: 0.99, -12.89]. Two of the studies (Konig, 1987; Chudry, 1987) reported data on the change in FEV1

following a third exercise challenge at 240 and 270 minutes, respectively, after pre-treatment. The pooled MWD in these studies was -5.66 (95% CI: 2.84, -14.17) These results suggest that the duration of the protective effect provided by NCS does not extend beyond 2 hours. (Appendix G, Figure 4.20)

**iii. Other effects**

Evaluation on subjective outcomes of interest were abandoned due to the lack of relevant reporting in the original publications. For example, this review could not examine the effects of NCS on symptom experience after NCS treatment or patient satisfaction with the drug. Despite successfully contacting many primary authors requesting information, additional information was not provided.

**iv. Adverse effects**

Data on side effects was not collected systematically. Twelve of the 20 (60%) studies commented on adverse effects. Seven of these 12 (58%) stated that no adverse effects or symptoms attributable to NCS were noticed in the period of time during which participants were observed. Five studies mentioned minor side effects which included a bad taste, throat irritation and cough (see Table of Included Studies, Appendix C). One study, (Henriksen, 1988) reported a mean increase in heart rate after NCS; however, this was not clinically significant (4 beats per minute). Increasing the dose of NCS did not appear to increase the side effects.

# Chapter five

## Discussion

### 5.1 Introduction

Exercise induced bronchoconstriction is a characteristic and frequent feature of asthma (Henriksen, 1988), often presenting a considerable problem for patients, especially when exacerbated by cold temperatures, air pollution, aeroallergens, and fog. Regular physical activity is important to health, but for those who suffer from EIB, exercise may be severely curtailed if it regularly leads to bronchial obstruction. The goals of clinical management are to utilise a combination of drug prophylaxis with other non-medical interventions that will permit participation in sports for both recreational and competitive athletes. For non-athletes, it is a matter of arriving at a therapeutic regimen that will allow a more normal range of physical activities in everyday life at work and at home. In all cases, the goal of management is to prevent exercise avoidance attributable to EIB.

Studies have shown that regular physical effort helps to increase aerobic capacity and to improve pulmonary function during the post exercise response (Oseid, 1995). It is well known that physical exertion can continue under the protection of $\beta_2$ agonists but these are unlikely to attenuate the underlying bronchial hyperreactivity; moreover, recent trials have cast doubt on the safety of regular $\beta_2$ agonist use by asthmatic patients (Cheung, 1992). Nedocromil has both anti-inflammatory and neuronal effects and it acutely protects against both specific allergen and exercise challenge (Bernstein & Bernstein, 1993). It avoids many of the pitfalls of $\beta_2$ agonists.

This thesis, based on a meta-analysis of twenty randomised, crossover trials that included 280 adults and children across eight countries, supports the single dose use of NCS as an effective pharmaceutical option for the management of EIB. NCS significantly inhibited bronchoconstriction, shortened the duration of EIB, and provided clinically significant protection over placebo. Of note, this effect was more

pronounced in those with more severe EIB. The pooled effect was homogeneous for age, dose, timing of pre-treatment, and delivery method. When NCS was given within an hour of an intense, prolonged exercise challenge, the severity of bronchoconstriction, measured by the change in FEV1 and PEFR, was significantly reduced, in the order of 16% (95% CI: 13, 18%), and 15% (95% CI: 8, 22%) respectively. There was evidence to indicate that the resultant EIB response was not only blunted over the entire post-exercise period, but was also of a shorter duration. These data indicated that, on average, people returned to normal lung function within 10 minutes of completing the exercise challenge. This degree of documented improvement provided a mean protection index of 51% (95%CI: 46, 55%), a level of protection that is considered to be clinically significant. The protective effect appeared to be in the order of 2 hours. NCS was well tolerated, the only adverse effects reported were minor complaints of throat irritations and an unpleasant taste was reported by a few.

## 5.2 Methodological strengths of the review

### 1. Trial inclusion, design, and quality

An extensive literature search was conducted without regard to language or publication status. Content experts were asked for additional trials, and reference lists of relevant literature were searched in order to assemble an unbiased selection of potentially relevant trials. The trials were independently selected and critically appraised, using objective, validated, criteria, by two reviewers. All of the included trials used a randomised, placebo-controlled, double blind, crossover design, and all were rated as having been conducted according to approved standards.

### 2. Populations

It is assumed, that in the majority of studies, the participants were selected from convenience samples of volunteers recruited from asthma clinics or asthma retreat centres. The studies included known asthmatics (aged 6 to 54 yr.) with stable lung function at the time of testing (FEV1 or PEFR > 70% of predicted values, with < 10

to 15% variability between challenges). Concurrent therapy included a variety of common anti-asthma agents, however, most medications were discontinued for periods of 6 hours to 1 week prior to each challenge to limit confounding influences. Despite these concurrent therapies, each individual demonstrated diagnosable EIB prior to inclusion in a trial by confirming a decrease in FEV1 or PEFR of at least 15%. The majority of participants had atopic tendencies but no other complicating medical conditions.

**3. Interventions**

The interventions studied were consistent across trials. The trials evaluated a range of NCS dosages from 1 to 8 mg delivered via MDI, either with, or without a spacer. The timing of administration varied from 15 to 60 min prior to a standardised exercise challenge of sufficient intensity and duration to induce EIB. Except for the three studies that evaluated the duration of the effect of NCS, all studies had the participants perform the exercise challenges on separate days (anywhere from consecutive days up to one week apart) at the same time of day. The challenges were performed indoors in controlled environments with temperatures between 17 to 24° C and relative humidity between 35 and 60%. The Oseid trial (1995) was performed at -18° C in dry air.

**4. Outcomes**

All studies reported outcomes using a consistent format. The change in pulmonary function was expressed as a percentage of the pre-challenge baseline, which is the most widely used guide to diagnose the severity of EIB (Anderson, 1983). Patients registered their greatest fall at different times ranging from 3 to 15 minutes post exercise. The point of the greatest decrease was compared to the pre-challenge baseline.

Side effects reported were relatively minor. NCS had no effect on the resting level of lung function, hence it did not prevent EIB through bronchodilation prior to the exercise challenge.

**5. Results**

The pooled effect was homogeneous for age, dose, timing of pre-treatment, and delivery method. These results are consistent with what is already known about NCS. Some studies have shown that spacer devices can increase the proportion of an aerosolised dose delivered to the lung (Crompton, 1995). This benefit was not realised in these studies, but that may be due to the fact that most participants were observed to use good inhaler technique regardless of the delivery system. A spacer would therefore not provide an additional advantage in such individuals.

## 5.3 Methodological limitations

There are no major issues that would limit the applicability of these results to a similar population, however, there are a few cautionary notes. The overall findings can be generalised to people who have asthma and atopy with stable lung function yet still exhibit confirmed reproducible EIB when exercising at a level of sufficient intensity and duration. People with EIB caused by other airway disorders were not studied.

All of the challenges took place in laboratories with controlled environments; consequently, the results need to be re-evaluated outdoors where environmental conditions have greater variability. Analysis adjusting for other confounding factors was not possible due to insufficient data.

There is a possibility of publication bias or study selection bias in the meta-analysis. A comprehensive, systematic search was undertaken to limit biased inclusion, still the possibility exists that we may have missed locating unpublished negative trials. If this were the case, we may be overestimating the effect of NCS treatment.

Only one author reported the number of patients excluded from the study prior to randomisation and there was no information on how those individuals differed from those who were included. It is impossible to know how this would influence the estimate of effect. However, since the effect is very robust considering the diversity of participants and settings, we are reasonably confident of the results.

In order to evaluate the effect of baseline severity on the results, the reviewers selected the mean maximum percent fall FEV1 or PEFR in the placebo group for comparison (to adjust for any placebo effect). This was the only subgroup comparison that demonstrated a significant difference in effect size. In planning a new primary study, stratifying by this variable may reveal additional information on NCS.

The analysis of lung function data was strengthened by the consistency of standardised reporting, which, in the majority of studies, included a measure of variance. Imputing missing standard deviations is a compromise for missing data; however, sensitivity analysis showed no statistically significant differences when comparing results using imputation to only those using recorded values. The small number of studies reporting PEFR results gives us pause, but the concordance with FEV1 results is reassuring.

Finally, all studies in this review used the crossover design, which bears further discussion. The concerns regarding the inclusion of crossover trails in a meta-analysis centre on three factors:, drug carry-over effects, period effects, and statistical issues. Since EIB is a short, transient condition that returns to baseline values within one hour, and NCS is a short acting agent, with rapid clearance from the body, and few side effects, we believe the potential for a carry-over effect to be negligible. Were it present, it would bias the treatment effect towards the null and give a more conservative estimate. The other two drugs evaluated in some trials, SCG and furosemide, are also extremely short acting compounds with negligible potential for a carry-over effect. Nonetheless, data were not reported in a manner that allowed analysis to confirm the presence or absence of a carryover effect. One author did provide the data. These data were analysed and showed no evidence of either a period or sequence effect. Three other authors reported in their publications, that sequence of treatment order did not influence the estimate of effect.

Period effect comes into play because EIB is a variable condition and it is possible that baseline PFT values could vary prior to each exercise challenge. Individuals could randomly experience a change in baseline airflow values depending on many of the

factors discussed in chapter one. This is why treatment sequences must be balanced and uniform (section 2.2.1). All studies, however, ensured that participants had lung function measures greater than 70% predicted values with less than 10 to 15% variability in an attempt to standardise for period effect. Had there been a period effect in every study, there would be no reason to believe any systematic bias towards any one period. The large number of studies included, coupled with the variations in ages, sex, country, severity, co-intervention, etc. should ensure an equal distribution of period effects if they exist. By averaging the estimates the period effect would disappear, leaving an unbiased estimate of the treatment contrast (Senn, 1991).

The literature search did not locate any parallel group studies in order to compare results from the two research designs. Future studies using the crossover method should concentrate on complete reporting of results by period and sequence to assure readers these concerns have been accounted for.

Information related to acceptable randomisation, allocation concealment, and blinded outcome assessment was not adequately reported in most of the studies. Since PFT measures, particularly the PEFR, are effort dependent, systematic error in performing and/or recording of outcomes could influence results in either direction.

Finally, data on symptom scores, exercise performance, or subject satisfaction were not included in the studies. The patient's own assessment of NCS is an important consideration in choosing one treatment over another.

## 5.4 Conclusions

A single dose of NCS inhaled 15 to 60 minutes prior to strenuous physical activity was effective in preventing deterioration in lung function during the immediate post-exercise period in adults and children with EIB. This benefit included a more rapid return to normal lung function.

A clear dose-response between 1 mg and 8 mg of NCS was not observed; most studies used 4 mg of NCS. It has been suggested that all of these doses lie at the top of the dose response curve for NCS (de Benedictis, 1995). Although there is no clear evidence of a dose response, this cannot be ruled out due to the paucity of studies in the low and high dose groups, creating large differences in the sample sizes being compared. There were insufficient data to examine the influence of increasing the dose of NCS according to baseline severity, but there was evidence from the subgroup analysis to suggest that NCS provides a greater protective effect in people with more severe EIB.

Though using a spacer did not modify the results obtained in this review, the use of such a device with an MDI helps people who fail to benefit from anti-asthma therapy due to poor inhaler technique (Comis, 1991)

Not only was NCS effective, on average, in attenuating the EIB response to a clinically significant degree, no appreciable adverse effects were demonstrated over a wide range of doses.

### 5.5 Areas for future research

Future study involving these trials should focus on analysing the individual patient data that was provided in nine of the studies. Though the data is limited in scope, authors have been asked to provide the original data from the trial for further analysis. The Cochrane methodology group is interested in comparing estimates and their precision when data is analysed as a parallel study, a crossover study, or as individual patient data.

Future research aside from these trials should focus on correlating the physiological benefits derived from NCS with other outcomes such as symptom scores, performance effects, patient preference, and cost. Validation of the dose-response relationship between those with milder EIB and those who suffer more severe obstruction must be

done. It would be useful to know if increasing the dose lengthens the duration of protection against a decrease in airflow in both responders and non-responders to NCS.

The time course of EIB as well as the rate of return to baseline estimates is still not clear, nor is the response to NCS in subjects with severe EIB. The latter should be studied in a parallel trial design.

It is still not clear which agent, among the many available (including NCS), is the most efficacious in the prevention of EIB. Considering the complex mechanisms involved in EIB, it may not be reasonable to look for a single drug to completely prevent bronchoconstriction. Trials directly comparing different agents should be conducted; alternatively, meta-analysis of the effect of different agents on EIB should be conducted, followed by trials comparing them singly and in combination. The low side effect profile of NCS suggests that long term use would not be contraindicated but studies comparing long term use and the effect on EIB are needed.

Finally, almost all trials studied illustrate the general need for improvement in the reporting of the recruitment procedures followed, the methodology used, and the analysis procedures. All outcomes reported should include an effect estimate accompanied by variance measures.

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# Appendix A

## Protocol

## Nedocromil sodium in the prevention of exercise-induced bronchoconstriction in asthma

# Nedocromil sodium in the prevention of exercise induced bronchoconstriction in asthma [protocol]

**Spooner C**

**Date of most recent substantive amendment : 22 November 1996**

**Date review expected : 31 August 1997**

## Background

Airway hyper-irritability that leads to airway narrowing following an exercise challenge is a phenomenon known as exercise induced bronchoconstriction (EIB). It occurs in 70% - 80% of people with asthma (1) and an estimated 12% -15% of the general population (2). Screening of athletes for the 1984 Summer Olympic Games revealed that 11.2% (67 of 597 athletes screened) had EIB (3).

EIB is characterized by a transitory increase in airflow obstruction that is provoked by 6 - 14 minutes of continuous, strenuous exercise (4). Post-exercise decreases of 10% to 20% in forced expiratory volume at 1 second (FEV1) or the peak expiratory flow rate (PEFR) indicate mild EIB, 20% to 40% moderate, and =F2 40% severe (1,5,8). The increased airflow obstruction causes dyspnea, cough, wheeze, premature fatigue and prolonged recovery times. Maximum bronchoconstriction typically occurs 5 to 15 minutes after exercise ceases and usually subsides spontaneously within 20 to 60 minutes (5).

The severity and impact of symptoms is dependent on several factors: the type, intensity and duration of activity; the climactic and environmental conditions; the overall control of asthma; the level of physical conditioning, and the time since previous exercise (6). Episodes can be severe enough to require rescue medication and even emergency treatment. As noted, EIB is a common phenomenon that concerns not only those who suffer from it, but parents, coaches, physical education teachers, physicians, and others who supervise physical activities. The problems caused by EIB can hinder participation in these activities and cause sub optimal performance levels. Considerable expenditures result from both health service utilization and pharmacological treatment. The etiology and pathophysiology of EIB are still being investigated and some issues remain unresolved (1,2). However, once the condition is diagnosed, the goal is to decrease and/or prevent EIB through both pharmacologic and non-pharmacologic interventions. The results of achieving control can be remarkable at all ages and levels of activity; for instance, the athletes with EIB at the 1984 Olympics won 41 medals (3).

Prevention of EIB has been the focus of therapy, therefore, emphasis is placed on interventions that are taken before exercise begins. Many different pharmacologic agents have proven to be useful in attenuating EIB but there remains considerable debate regarding the merits of each treatment, the optimal dose, and the method of delivery. Traditionally, inhaled beta-agonists and other bronchodilating agents have been the drugs of choice (7). Recently, inhaled inflammatory mediators such as nedocromil sodium (NS), sodium cromoglycate (SCG), and corticosteroids have gained favor. Other drugs including

antihistamines, furosemide, heparin, calcium-antagonists, theophyllines and leukotriene antagonists have been evaluated.

This systematic review examines the available evidence from randomized, placebo -controlled trials evaluating NS as a pre-exercise intervention medication to attenuate exercise- induced bronchoconstriction. To date, no systematic overview of the effect of NS on attenuation of EIB has been published.

## Objectives

The objective of this review is to determine, quantitatively, the effect of administering an inhaled form of NS prior to a strenuous exercise challenge on those who suffer from EIB. The degree of effect and the duration of any effect will be assessed from studies that compare NS to a placebo. Outcomes examined will include physiologic measures such as pulmonary function, heart rate, respiratory rate, oxygen consumption, plus participant satisfaction, physical performance, as well as side effects or disadvantages. We will use the following criteria to define exercise induced asthma: Post-exercise decreases of 10% to 20% in FEV1 or PEFR indicate mild EIB, 20% to 40% moderate, and 40% severe EIB (1,5,8).

## Criteria for considering studies for this review

### Types of participants

Studies where participants have demonstrated that they have EIB prior to entry into the trial will be considered for inclusion. Studies recruiting children, adolescents and/ or adults will be reviewed and these designations will form subgroup analyses.

The severity of EIB experienced is dependent on the type, intensity, and duration of the exercise challenge; the climactic and environmental considerations; and individual factors, distinctions will be made amongst studies that differ in these areas and subgroup analyses will be performed.

A priori, the reviewers plan subgroup analyses on the following participant features:
1. Age: those < 14 years, those =F2 14 years.
2. Gender
3. Physical health/condition

Final distinctions and cut points will be steered by the groups studied in the included trials.

### Types of intervention

The primary focus will be on studies where participants are randomized to receive either NS or placebo prior to undergoing a standardized exercise challenge test.

A priori, the reviewers plan subgroup analyses on the following treatment characteristics:
1. Dose of drug given
2. Delivery system used: Pressurized aerosol (MDI) with or without a spacer, nebulization
3. Timing of pre-medication
4. Features of exercise challenge test

Final distinctions and cut points will be steered by the methods used in the

included trials.

Studies that have more than one drug arm will be included if there are results that contrast NS vs. a placebo distinctly reported. Only this arm will be included. Studies that involve delivery via nasal sprays will not be included.

### Types of outcome measures

All outcomes, both subjective and objective, will be considered. The main outcome for the studies will be continuous data from physiologic measures:
pulmonary function tests (PFTs) (e.g. FEV1, FEF 25-75, PEFR, FVC), heart rate, respiratory rate, O2 consumption, time to return to baseline PFTs.
Secondary outcomes will include: a) symptom scores, b) subjective reports of well-being, c) exercise performance, d) any report of adverse outcome.

Attempts will be made to contact the primary investigators of studies to determine willingness to provide missing information or to clarify data.
Data will be extracted and analyzed on intention to treat basis.

### Types of studies

To be considered for inclusion, the clinical studies must be randomized, placebo - controlled trials.

## Search strategy for identification of studies

See: Collaborative Review Group search strategy

1. The Cochrane Airways Group has developed an "Asthma and Wheez* RCT" database through a comprehensive search of Embase (1980 - present), Medline (1966- present), and CINAHL (1982- present). In addition, hand searching of the top 20 respiratory care journals has been completed and relevant articles included. A preliminary search of this database will be completed using the following terms:
a) Asthma OR Wheez* AND exercise*

Further searches will be completed using the following terms:
a) Asthma OR Wheez* AND
b) exercise OR exercise induced* AND
c) Nedocromil* OR Nedocromil Sodium* OR Tilade OR NS*

Randomized controlled trials are identified in the register using the following search strategy: (placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study). There will be no restriction to language of the publication, attempts will be made to translate the articles from the foreign language literature.

2. Reference lists of each primary study and review article will be checked to identify additional potentially relevant citations.

3. Inquires regarding other published or unpublished studies known and/or supported by the authors of the primary studies will be made and results included in this review.

4. Personal contact with colleagues, collaborators and other investigators working in the field of asthma will be made to identify potentially relevant studies.

## Methods of the review

1. The preliminary search for all trials which appear potentially relevant

will be conducted by one reviewer (CHS)

2. All trials which appear relevant will be selected for full review by two reviewers (CHS, BHR)

3. Two reviewers will independently select trials for inclusion using the full study and standardized inclusion criteria. (They will not be blinded to the author, title, etc.). Agreement will be measured using simple agreement and kappa statistics. Disagreement will be resolved by consensus or if necessary, third party adjudication. The independent reviewers will document the content of each included study.

4. Two reviewers will independently assess the methodological quality of each included study by using two methods: First, the Cochrane Collaboration approach to assessment of allocation concealment, all trials will be scored and entered using the following principles:
Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment
Inter-rater reliability will be measured by using simple agreement and kappa statistics.

Second, each study will be assessed using a 0-5 scale described by Jadad (1995) and summarized as follows:
1) Was the study described as randomized (1=3Dyes; 0=3Dno)?;
2) Was the study described as double-blind (1=3Dyes; 0=3Dno)?;
3) Was there a description of withdrawals and dropouts (1=3Dyes; 0=3Dno)?;
4) Was the method of randomization well described and appropriate (1=3Dyes; 0=3Dno);
5) Was the method of double blinding well described and appropriate (1=3Dyes; 0=3Dno)?;
6) Deduct 1 point if methods for randomization or blinding were inappropriate.

Inter-rater reliability will be measured by using simple agreement, kappa, and weighted kappa statistics.

Data from the trials will be extracted by one of the reviewers (CHS). Confirmation from the primary author(s) on accuracy and completeness will be obtained when possible. If the authors are unable to respond, a second reviewer will independently extract data. Disagreement will be resolved by consensus. The data will be entered into the Cochrane Collaboration software program (Review Manager).

STATISTICAL CONSIDERATIONS

All trials will be combined using the Review Manager (Revman Version 3.0). Comparisons will include:

Comparison 1.0: NS (any delivery system) vs. Placebo

Outcome: PFTs
Subgroups:
1) younger children ( < 14 years old)
2) adolescents and adults

Outcome: Other physiologic measures
Subgroups:
1) younger children ( < 14 years old)
2) adolescents and adults
Outcome: Time to return to baseline
Subgroups:
1) younger children ( < 14 years old)
2) adolescents and adults

Outcome: symptom scores
Subgroups:
1) younger children ( < 14 years old)
2) adolescents and adults

Outcome: physical performance measures
Subgroups:
1) younger children ( < 14 years old)
2) adolescents and adults

Outcome: adverse effects
Subgroups:
1) younger children ( < 14 years old)
2) adolescents and adults

Other comparisons using the same subgroups as above:
Comparison 2.0: NS via MDI vs. placebo

Comparison 3.0: NS via nebulization vs. Other drug

Comparison 4.0: NS (any delivery system) vs. other drug - single comparison only. We will divide if heterogeneity exists.

After computing appropriate tests, if significant heterogeneity exists in design, intervention, population, or outcome, the groups will be divided on the following basis:
a) Methodological quality (Jadad criteria 4 or 5 vs. papers scored < 4);
b) Exercise challenge (duration, intensity, type);
c) Dose of NS administered
d) Climactic, environmental conditions
e) Method/criteria of determining symptoms, PFTs or both).

## References

*There are no references on file for this review.*

## Coversheet

### Title

Nedocromil sodium in the prevention of exercise induced bronchoconstriction in asthma

### Short Title

Nedocromil sodium and exercise induced asthma

### Reviewer(s)

Spooner C

**Date of most recent amendment :** 19 March 1997

**Date of most recent substantive amendment :** 22 November 1996

## This protocol should be cited as :

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**Sources of support to the review**

- *None on file*

For information on the editorial group see:
Cochrane Airways Group

## Keywords

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# Appendix B

**Working document**

**Criteria for Inclusion**

## NEDOCROMIL SODIUM TO ATTENUATE EXERCISE INDUCED BRONCHOCONSTRICTION (EIB)

### CRITERIA FOR INCLUSION

**CITATION #:** **|REVIEWER:**

Please assess each paper using the following criteria. Place a check (✓) beside the criterion you feel best describes the paper. A paper needs to fit only one exclusion criterion to be rejected. Indicate why excluded.

**1) DESIGN:**

[ ] Include if a randomized, controlled, clinical trial on adults and/or children. (cross-over studies are acceptable if randomised in the first arm)

[ ] Exclude if study non-experimental (cohort, case-control, before/after studies, not controlled)

**2) POPULATIONS:**

[ ] Include if all participants in the study were reported to have EIB. This could mean it was stated in the introduction, or methods, that they had a history of EIB, or it could be documented in a table or graph of baseline values at an initial screening or control test. (Table or graph must show a decrease in FEV1 or PEFR of >10%).

[ ] Exclude papers where patients have asthma but is **not known** if they have EIB.

**3) INTERVENTION:** Nedocromil sodium (NCS) or Tilade®

[ ] Include if trial used any form of inhaled NCS[1] given independently as pretreatment before a standardized exercise challenge for EIB and compared to a placebo.
([1] i.e. metered dose inhaler, with or without a spacer, nebulized)
A multiple arm study can be accepted if there is data comparing NCS to placebo.

[ ] Exclude if NCS was not the primary research intervention. Exclude if NCS given in **combination with** another treatment.

**4) OUTCOMES:**

[ ] Must have EIB defined and reported in objective measures. e.g. Pulmonary function tests such as: PEFR, $FEV_1$

[ ] Exclude studies that do not include standardized objective outcome measures.

**5) FINAL DECISION:**

[ ] **INCLUDED** (meets inclusion criteria above)

[ ] **NOT INCLUDED: Why?**

[ ] **CAN'T TELL** (need more information from authors)

# Appendix C

## Table of Included Studies

## Table of Characteristics of Included Study

## Characteristics of Included Studies

**Nedocromil sodium as single dose prophylactic treatment of exercise-induced bronchoconstriction: a meta-analysis**

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| Boner, 1988 | RCT (coding sheet), double-blind, crossover trial. One screening day, 4 test days at same time of day. No withdrawals or dropouts. Concomitant Tx:none on steroids in last 3 mon. Stopped SCG & slow release preparations for 1 wk., bronchodilators (BD) for 12 hrs. pre test. None on steroids in past 3 mon. Exercise test: inclined treadmill, 6 min, heart rate = 86-94% predicted max. for age. | Italy. Recruitment: a residential home for asthmatic children. N=13: 9 m, 4 f. Age: 7.5-13 (mean 10 yrs) Inclusion: stable asthma, clinical history of EIB (fall FEV1 at least 15%), atopic, proper inhaler technique. | From randomised code sheet: NCS 4 mg or matching placebo via MDI using Auty-Alkounyan spacer device or normal adapter 15 min pre-exercise test. | PEFR and FEV1 pre Tx, 5 & 10 min post Tx then at 1, 3, 5, 7, 10 & 15 min (some 25 ) post test. Calculated Max % change FEV1, % protection. Side effects: nothing unusual was reported during the study. | Jadad score =4<br>Author confirmed data extraction within limits, could not access old data.<br>Mean, SD calculated from individual patient data.<br>Time course data: estimated from graph and table. |
| Boner, 1989 | RCT, double-blind, crossover trial. One screening day, 2 test days. No withdrawals or dropouts. Concomitant Tx: 17 on SCG, 3 on ICS, all on BD, 2 on OBD. Stopped SCG, ICS, BD for 24 h, long-acting BD for 8 h, short-acting BD for 6 h. pre test. Exercise test: inclined treadmill, 6 min, heart rate = 170-180. T=21-23 C, RH = 50-60% | Italy. Recruitment: a residential home for asthmatic children. N=20: 15 m, 5 f. Age: 7.5-15 (mean 11.3 yrs) Inclusion: asthmatic, atopic, EIB (fall FEV1 at least 15%) mean 39.9%. | In randomised order in matching inhalers: NCS 4 mg (2x2 mg) or placebo (2 puffs, propellant only) via MDI 30 min pre-exercise test. | Used Vitalograph spirometer. Measured: PEFR, FVC, FEF 25-75, and FEV1 5 min pre Tx, 5, 10, 20 & 25 min post Tx, then at 5 min intervals for 30 min. post test. Mean of pre- test readings used as baseline. Calculated: Max % decrease in lung function as % of pre-test baseline. % protection. Side effects: stated ' no unusual symptoms or adverse reactions reported.' | Jadad score = 4<br>Treatment order had little influence on results.<br>Author confirmed data extraction within limits, could not access old data.<br>Time course data estimated from graph.<br>Use pooled SD from other studies |
| Bundgaard, 1988 | RCT, double- blind, crossover. Tested at same time of day on consecutive days over 1-2 wks. No withdrawals or dropouts. Concomitant TX: 5 on theophylline, 9 on ICS, 1 on OCS, 10 on BD, 1 on chronic oral bronchodilators (OBD) all others had not had steroids in last 3 mon. Stopped theophylline for 24 h, BD for 12 h. Continued ICS (9pts), 1 on OCS. All given BD | Denmark. Recruitment: (not described) N=14: 6 m, 8 f. Age:21-49 mean=31 sd 7.3. Inclusion: stable asthma, reproducible EIB (fall in PEF > 20%). lung function within 15% predicted normal at time of exercise test. Excluded if pregnant. | Randomised to: NCS 2 mg or 4 mg or placebo 2 puffs via identical MDIs 30 min pre test. Monitored technique. | Measured: PEFR 5 & 10 min pre Tx, post Tx then 3, 5, 10, 15, 20, & 30 min post test. (max of 3 readings) Calculated: Max % fall PEFR, mean % fall PEFR at time points. Side effects: Stated 'no Adverse effects reported.' Minor reactions: coughing (2) all Tx, dry throat (1 - placebo) itching throat (1 - 4 mg NCS), taste (5 NCS, 1 pl). Reversal BD tx given within 15 min to 8 taking placebo, 3 taking NSC 2 mg & 2 taking 4 mg as | Jadad score = 4<br>No author contact to date.<br>Some baseline characteristics outlined in a table. |

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| | at 30 min post test or sooner if steady low PEFR reached. Exercise test: treadmil, 6 min, T=10C, RH = 45%, Speed adjusted to cause fall in PEF of 20-30%. | | | part of study protocol. | |
| Chesky, 1987 | RCT, double-blind, crossover. Two study days in 1 wk., serial tests on same day: 1 control test, 90 min later randomized to Tx then tested at 30, 130 and 270 min post tx. Concomitant Tx: Stopped SCG, theophylline, IHD 12 hr pre test. Allowed steroids. Exercise test: inclined treadmill, 6 min, HR=170. Ambient room temp. | UK. Recruitment: Asthma clinic. N=12, 9 m, 3 f. Age 8-15 yrs. mean 13.9. Inclusion: Stable Asthma, history of EIB (fall in FEV1 > 20%), good inhalation technique. | (from pharmacy) In randomized order NCS 4 mg or placebo via identical MDI 30 min pre exercise test. | Used rolling seal spirometer. Measured FEV1 pre and post tx and various times post exercise. Calculated max % fall FEV1, % protection. | Jadad score = 3<br>There was a significant decline in severity of EIB over course of tests independent of Tx. Author provided confirmation of randomization and concealment, and absolute numbers and standard deviations not reported in article. |
| Comis, 1993 | RCT, double-blind, crossover. 7 study days. Tests performed at same time daily (each patient completed within 10 days). Concomitant Tx :Inhaled medications. Stopped ICS & SCG for 1 wk., IHD 12 h pre test. Exercise test: inclined treadmill, 6 min, Pulse = 180, T=22-25 C. RH=35-45%. | Italy. Recruitment: residential school for asthmatics. N= 12: 7 m, 5 f. Age: 6.5 - 13.5 (mean 11 yrs) Inclusion: Asthmatic, atopic, history of EIB (fall in FEV1 > 15%) | Randomized to NCS 4 mg, SCG 10 mg, or placebo via MDI alone or with a 700 ml spacer 30 min pre test. Placebo=propellant only. Inhalation technique supervised. | Used a Vitalograph compact spirometer. Measured FEV1 before Tx, 30 min after Tx and at end exercise, then 1, 6, 11, 16, 21, 26, 30 min post test. Calculated max % fall in FEV1, % protection. Adverse effects: not mentioned. | Jadad score = 3<br>Author confirmed data extraction within limits, could not access old data. |
| De Benedictis, 1994a | RCT, double-blind, crossover. Screening plus 3 tests at same time on separate days, completed within 10 days. No withdrawals or dropouts. Concomitant Tx: theophylline, IHD, SCG, NCS, ICS. No OCS. Stopped theophylline for 24 h, other drugs for 12 h before each test. Exercise | Italy. Recruitment: pediatric asthma clinic. N=17: 11 m, 6 f. Age: 7-15 mean 10.2 +/- 2.2 yr. Inclusion: asthma, reproducible EIB (fall in FEV1 at least 15%) Baseline FEV1 > 70% predicted normal and varied < 10% from previous study day. No RI in previous 4 wks. | Random, blinded order: NCS 4 mg or SCG 10 mg or placebo via MDI (2 used a spacer) using closed lip technique 20 min pre exercise test. | Used: turbine spirometer, & Knudson's predicted values. Measured: FEV1 pre Tx, pre-exercise then 3, 5, 10, 15, 30 min post exercise. Pulse monitored pre/post exercise. Calculated: Max % fall in FEV1, % protection. Adverse effects: not mentioned. | Jadad score = 3<br>Author contacted but has not confirmed data to date. Time course estimated from graph. |

## Characteristics of Included Studies (continued)

**Nedocromil sodium as single dose prophylactic treatment of exercise-induced bronchoconstriction: a meta-analysis**

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| | test: inclined treadmill, 6 min, pulse=85% of max predicted for age. T=21-23C, RH 48-58%. | | | | |
| De Benedictis, 1994b | RCT, double-blind, crossover. Screening plus 3 test days at same time on separate days, completed within 10 days. No withdrawals or dropouts. Concomitant Tx: theophylline, IHD, SCG, NCS, ICS. No OCS. Stopped theophylline for 24 h, other drugs for 12 h before each test. Exercise test: inclined treadmill, 6 min, pulse=85% of max predicted for age. T=21-23C, RH 48-58%. | Italy. Recruitment: pediatric asthma clinic. N=8 children, 5 m, 3 f. Age: 7-11 (mean 8.7) Inclusion: asthmatic, reproducible EIB (fall in FEV1 at least 15%), baseline FEV1 > 70% predicted normal and varied < 10% from previous study day. No RI in previous 4 wks. | Randomised to: NCS 4 mg or SCG 10 mg or placebo via MDI with Aerochamber spacer 20 min. pre exercise test. Inhalation technique monitored. | Used turbine spirometer & Knudson's predicted values. Measured: FEV1 pre Tx, pre-exercise then 3, 5, 10, 15, 30 min post exercise. Pulse monitored pre/post exercise (not reported as an outcome). Calculated: Max % fall in FEV1 %, % protection Adverse effects: not mentioned. | Jadad score = 3<br>Author confirmed mean % fall NCS = 14.8 SD 18.6<br>Author contacted but has not confirmed data to date. |
| De Benedictis, 1995 | RCT, double-blind, crossover. Screening plus 3 test days at same time on separate days, completed within 10 days. No withdrawals or dropouts. Concomitant Tx: theophylline, IHD, SCG, NCS, ICS. No OCS. Stopped theophylline for 24 h, other drugs for 12 h before each test. None on oral steroids. Exercise test: inclined treadmill, 6 min, pulse=85% of max predicted for age. T=21-23C, RH 48-58%. | Italy. Recruitment: pediatric asthma clinic. N=13: 9 m, 4 f. Age: 7-15 (mean 10 sd 2.3) Inclusion: asthmatic, reproducible EIB (fall in FEV1 at least 15%), baseline FEV1 > 70% predicted normal and varied < 10% from previous study day. No RI in previous 4 wks. | Random, blind order: NCS 4 mg or SCG 10 mg or placebo via MDI using closed lip technique 20 min & 140 min pre exercise test. Technique monitored. | Used: turbine spirometer & Knudson's predicted values. Measured: FEV1 pre Tx, pre-exercise then 3, 5, 10, 15, 30 min post exercise. Pulse monitored pre/post exercise. Calculated: Max % fall in FEV1, % protection. Adverse effects: not mentioned. | Jadad score = 3<br>Author stated that subjects in these three studies were discrete individuals. |
| Dubelic, 1986 | RCT, double-blind, crossover. Screening plus 2 test days at same time on separate days, completed within 5 days. No withdrawals or dropouts. Concomitant Tx: not mentioned. Exercise test: Free running in corridor at room temp. | Germany. N=12: 7 m, 5 f. Age: 14-19 (mean 16.9) Inclusion: atopic, bronchial hyperreactivity, reproducible EIB (fall in FEV1 > 20%) Baseline FEV1 > 70% normal values. | Randomised : NCS 4 mg vs placebo via MDI 30 min. pre exercise test | Measured: FEV1 pre Tx, 10 & 20 min post Tx, then 1, 3, 5, 10 min post exercise. Calculated: Max % fall FEV1, % protection. Adverse effects: Stated 'no side effects observed. | Jadad score = 3<br>Time course data calculated from graphs.<br>Max % fall FEV1 estimated from graphs<br>Used pooled sd from other studies |

## Characteristics of Included Studies (continued)

**Nedocromil sodium as single dose prophylactic treatment of exercise-induced bronchoconstriction: a meta-analysis**

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| | | | | | Author contacted |
| Henriksen, 1988 | RCT, double-blind, crossover. Control plus 2 test days no more than 1 wk. apart. No withdrawals or dropouts. Concomitant Tx: all on IHD, 4 on SCG, 2 on theophylline, 2 on OHD, 1 on ICS. Stopped oral anti-asthma drugs & SCG for 24 h, IHD for 12 h before each test, ICS continued. Exercise test: Treadmill, 5-6 min, HR = 180. Work load 2.8-3.4 watts/kg body wt. Used a nose clip. T & RH measured. | Denmark. Recruitment: not described. N=12, 10 m, 2 f. Age: 7-14 (mean 10.8) Inclusion: atopic, had perennial episodes of airway obstruction, history of EIH (fall in FEV1 at least 20%) baseline PEFR or FEV1 not less than 70% predicted normals. | Randomised to: NCS 4 mg or placebo via identical MDI's 30 min pre exercise test. | Used: Wright's PEF meter and electronic spirometer. Measured: FEV1 & PEFR, best of 3 readings, pre & post Tx, 10 & 5 min pre exercise, then at 2, 5, 10, 20, 30 min. post exercise or until maximum fall recorded. All terminated with IHD at 30 min or earlier if required. Calculated: Max % fall PEF or FEV1, % protection, effect of treatment order, effect on heart rate. Adverse effects: stated 'no unusual symptoms or adverse reactions were reported'. | Jadad score = 4<br>Tx order had no effect on result.<br>Small but significant increase in heart rate with NCS treatment over control run.<br>SD for mean max % fall FEV1 imputed from pooled results of other studies.<br>SD for mean max % fall PEFR calculated from individual patient data in article.<br>No author contact to date. |
| Konig, 1987 | RCT, double-dummy, crossover. Control plus 3 test days at same time of day, completed in 10 days. Participant performed 3 exercise tests on each study day. No withdrawals or dropouts. Concomitant Tx: theophylline, IHD. Stopped theophylline for 48 h, IHD for 12 h before each test. Exercise test: Inclined treadmill, 6 min. HR = 90% max predicted for age. T = 21.3-21.5, RH=48 - 50.4 % | USA. N = 12 m. Age: 21-38 (mean 27.3) Inclusion: asthmatic, reproducible EIB (fall in FEV1 at least 20%), baseline FEV1 > 70% normal, no URI's inlast 3 wks. Excluded if on SCG or oral steroids in last month. FEV1 varied <15% between test days. | In random order: 1) NCS 4 mg MDI plus placebo spinhaler capsule. 2) placebo MDI plus SCG 20 mg spinhaler capsule or 3) placebo MDI plus placebo spinhaler capsule 20 min. pre exercise test. Technique monitored. Test repeated at 2 & 4 hrs post Tx. | Used a wedge spirometer & Knudson predicted values. Measured: FEV1, FVC, FEF 25-75. pre Tx, 20 min post Tx, then 3, 5, 10, 15, 20, 30 min post exercise. Ex Test repeated with out medication at 120 & 240 min post Tx. Calculated: Max % fall FEV1, % protection. Adverse effects: none | Jadad score = 3<br>Repeated challenges at 2 hr intervals did not affect degree of EIH.<br>No author contact to date. |
| Mihalyka M S, 1988 | RCT, double blind, crossover. No withdrawals or dropouts. Concomitant Tx: Stopped IHD, SCG IH for 5 h, oral medications for 12 h pre test. Exercise test: treadmill running, 8 min, room air | Australia. Recruitment:not described. N=14 (sex not reported). Age:15 - 45 Inclusion: stable asthma, history of EIH (fall in PEFR at least 20%) | Randomised to: NCS 4 mg or placebo via MDI 15 min pre-exercise. | Used: Minato Spirometer. Measured PEFR pre exercise, post exercise. Only max % fall reported. Calculated: max % fall PEFR. Pulse recorded. Adverse effects: bad taste (4) | Jadad score =3<br>No significant difference in heart rate<br>Author provided unpublished individual patient data. |

## Characteristics of Included Studies

**Nedocromil sodium as single dose prophylactic treatment of exercise-induced bronchoconstriction: a meta-analysis**

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| Morton, 1992 | RCT, double-blind, crossover. Screening plus 4 study days at same time of day, completed in 11 days. Concomitant tx: SCG, IHD, ICS. Stopped IHD for 4h, long-acting BD for 12h , SCG, theophylline, & H1 antagonists for 24 h. pre test. Continued on inhaled steroids if had been on them at least 4 wks. 3 excluded because fall in FEV1 < 15% with all Tx. No dropouts. Exercise test: Inclined treadmill, 8 min. at 70% VO2 max. T = 20 +/- 2 C, RH = 40 - 54%. No food or fluid 2 h pre-test, allowed only 1 cup of caffeinated fluid or 1 chocolate bar on test day, avoided vigorous exercise for 24 h and total abstinance from exercise for 4 h pre-test. Exercise test: Inclined treadmill, 8 min, VO2 ~ 70% max | Australia. N = 16, 10 m, 6 f. Age: 13-30 (mean 20, sd 4.84) Inclusion: asthmatic, non-smokers, history of EIB ( at least a 15% fall in FEV1) FEV1 > 75% personal best. 2 m & 1 f excluded on this basis) 16 analyzed. Excluded if on ICS in last 4 wks. | Random assignment to NCS 8 mg, SCG 4 mg, placebo (propellant gas & sorbitan trioleate) or no TX via identical MDI's 15 min. pre-exercise test. Technique monitored. | Used a single wedge dry spirometer (highest of 2 trials). Measured: FEV1 pre-Tx, pre-exercise and immediately then 5, 10, 15, 20, 25 & 30 min. post exercise. Calculated: max % fall FEV1, % protection. Adverse effects: 12/16 said NCS had unpleasant taste, 1/16 said placebo did, 3 said NCS caused throat irritation. | Jadad score = 4<br>Author contacted. |
| November, 1994f | RCT, double-blind, crossover. Screening plus 4 test days at same time of day, every other day, completed over 3 wks. in Jan. - Feb. No withdrawals or dropouts. Concomitant tx: all on IHD, 6 on SCG or NCS, 2 on ICS, 4 on theophylline. Stopped oral BD & long acting BD for 12 h., short acting BD for 6 h. Exclusions: those on SCG or inhaled steroids in past month. Exercise test: Inclined treadmill, 6 min, HR = 170-180, T = 20-22 C, RH =45-50% | Italy. Recruitment: not described. N = 24, 16 m, 8 f. Age: 6-16. Inclusion: asthmatic, atopic, no URI in past 3 wks. History of EIB (fall in FEV1at least 15%) Excluded: those on SCG or ICS in past month. | In random order: 1) NCS 4 mg via MDI with large vol. spacer plus placebo (NS) x 15 min. via jet nebulizer. 2) Placebo (propellant only) MDI plus furosemide 30 mg neb. 3) NCS via MDI plus furosemide neb. 4) Placebo MDI plus placebo neb. | Used a pneumotacograph & predicted values from Zapletal et al. Measured: FEV1, PEFR, FEF15-75 pre-Tx, pre-exercise test then 2, 4, 6, 8, 10, 15, 20, 30 min post ex. Calculated: max % fall FEV1, PEFR and FEF25-75, % fall FEV1 at different time points, % protection. Adverse effects: NCS - unpleasant taste 6, mild throat irritation 3. Furosemide - none. Placebo - headache 1. | Jadad score = 3<br>'Treatment order had had little influence on results'<br>No author contact to date. |

## Characteristics of Included Studies

**Nedocromil sodium as single dose prophylactic treatment of exercise-induced bronchoconstriction: a meta-analysis**

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| Novembre, 1994a | RCT, double-blind, crossover. Screening plus 3 test days at same time of day,separate days. No withdrawals or dropouts. Concomitant tx: All on IHD, 6 on SCG, 3 on theophylline, 2 on ICS. Stopped IID & long acting IID's for 12 h., short acting IID's for 6 h. Exercise test: Inclined treadmill, 6 min, HR = 170-180, T = 20-22 C, RH =45-50%. | Italy. Recruitment: not described. N = 19. 13 m, 6 f. Age: 6-15. Inclusion: asthmatic, atopic, history of EIB (Fall in FEV1 at least 15 %), no URI in past 3 wks, FEV1 > 92% predicted normal at time of testing. Exclusion: SCG or inhaled steroids in past month. | In random order: NCS 4 or SCG 10 or placebo via MDI plus large volume spacer 20 min pre-exercise test. Technique monitored. | Measured with pneumotacograph. Measured: FEV1, PEFR, FEF15-75 pre-Tx, pre-exercise test then 1, 5, 10, 15, 20 min post ex. Calculated: max % fall FEV1, PEFR and FEF25-75, mean % fall FEV1 at time points, % protection. Adverse effects: NCS - unpleasant taste 4, SCG - unpleasnt tast 2. | Jadad score =3 No author contact to date. Time course data from table with sd reported |
| Oseid, 1995 | RCT, double-blind, crossover. 2 screen days, 2 study days, at same time of day on consecutive days. One withdrawal post placebo due to worsening asthma. (did not do NCS TX and not analysed). Concomitant Tx: IHD, 2 on ipratropium bromide, 7 on SCG, 1 on theophylline. Stopped: Astemizole for 3 wks, SCG or antihistamines for 3 days, OHD and ipratropium for 12 h, IHD for 8 h pre-test. Sustained release IID changed to short-term oral IID 1 wk per-test. Exercise test:bicycle ergometer, 8 min. Work efort monitored (70% VO2 max). T= -18+-5 C, dry air | Norway. Recruitment: clinic. N = 20. 6m, 14 f. Age: 15-28 (mean 18.9 +-3.73) Inclusion: stable asthma, atopic, non-smokers, history of EIH exacerbated by cold air, ( fall FEV1 > 20%) current FEV1 > 75% predicted, mild to moderate BHR (PC20 methacholine <8.0 mg/ml). Excluded: pregnancy, nocturnal asthma, clinically relevant diseases, no OCS or ICS in past 3 mo. | In random order: NCS 4 mg or placebo via identical MDI's 30 min pre-exercise test. Placebo = sorbitan trioleatesurfactant & chlorofluorocarbon propellant). Technique monitored. | Measured: FEV1, FVC, FEF25-75. pre tx then 5 & 29 min post TX then 0, 3, 6, 10, 15, 20 min post exercise. Calculated: Max % fall FEV1, % change at each time point. Adverse effects: one 3 h migrane headache post placebo. | Jadad score = 4 No author contact to date. |
| Roberts, 1985 | RCT, double-blind, crossover. Control plus 3 test days, same time of day, separate days. No withdrawals or dropouts. Concomitant Tx: 10 on SCG, 14 on IHD, 1 on IB, 3 on ICS. Stopped SCG for 24 h & IHD's for | Glasgow, UK. Recruitment: not described. N=9 (6 m, 3 f) Age: 16-50 (mean 31.1) Inclusion: asthmatic, atopic, history of EIB (fall in FEV1 at least 20%). | Randomised to :NCS 2 mg or 4 mg or placebo via identical MDI 30 min pre-exercise test. | Used a dry spirometer. Measured: FEV1, Pre Tx, 25 min post Tx then 2, 5, 10, 15, 20, 30 min post exercise. Calculated: % fall FEV1. Adverse effects: none complained of. | Jadad score = 4 No author contact to date. |

## Characteristics of Included Studies (continued)

**Nedocromil sodium as single dose prophylactic treatment of exercise-induced bronchoconstriction: a meta-analysis**

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| | 12 h pre-test. Continued on ICS. None on oral steroids. Exercise test: inclined treadmill, 5-8 min, P = 170, T = 20-22 C, RH = 40 - 60 % | | | | |
| Shaw, 1985 | RCT, double-blind, crossover. No withdrawals or dropouts. Control plus 2 study days 1 wk apart. Concomitant Tx: inhaled medications only. Stopped ICS, SCG for one wk, IHD for 8 h pre test. Exercise test: inclined treadmill, 6-12 min, until FEV1 decreased by > 15%. Ambient room temp and humidity. | UK. Recruitment: not described. N=8 m. Age: 17-47. Inclusion: asthma, non-smokers, atopic, history of EIB (fall in FEV1 at least 15%), pre test FEV1 ranged from 45-115% predicted (mean 86%) | Random order: NCS 2 mg or placebo via identical MDI's 20 min pre-exercise. | Used a Vitalograph. Measured FEV1, FVC pre Tx, pre-exercise then 2, 5, 10, 15, 20,& 25 min post exercise. Calculated: mean % fall FEV1 at time points, Side effects: none experienced. | Jadad score = 4<br>Use individual patient data to calculate mean max % fall FEV1 and SD<br>No author contact to date. |
| Sinclair, 1990 | RCT, (coded in pharmacy) double-blind, crossover. Tests on 3 successive days between 9:30 - 11:30 AM). Concomitant Tx: not described. Stopped IHD's for 24 h pre test. Exercise test: inclined treadmil, 6 min, T 17-25 C | UK. Recruitment: not described. N=20. 18 m, 2 f. Age: 17-28, mean 20.7. Inclusion: reproducible EIB (fall % FEV1 at least 15%) Exclusion: those on OCS, ICS, NCS or SCG. | Randomised to: NCS NCS 4 mg, SCG 10 mg or placebo via coded MDI's 30 min pre exercise. | Used Vitalograph. Measured: FEV1 pre exercise then 1, 3, 5, 7, 9 min post exercise. Calculated: mean % fall FEV1 at time points. | Jadad score = 5<br>Author contacted. Unable to provide further information. SD imputed as pooled estimate from other studies |
| Todaro, 1993 | RCT, double-blind, crossover. Concomitant Tx: none on chronic tx. Stopped SCG, IHD for 24 h pre test. Exercise test: based on the type of sport practiced. Work effort monitored. t 19-25 C. RH 45-52% | Italy. Recruitment: high level athletes - 7 on olympic team. N=13. 11 m, 2f. Age: 19-31 (mean 25). Inclusion: well documented EIB (fall FEV1 >=10%,all 13 were > 15%). FEV1/FVC range 60.3 - 87.8 (mean 70.2 SD 8.0) | In random order to: NCS 4 mg or placebo via MDI 20 min pre exercise test. | Used: turbine spirometer. Measured: FEV1 pre tx, pre exercise then immediately and 5, 10, 15, 20, 30 min post exercise. HR monitored. Calculated: max % fall FEV1, mean fall % FEV1 at time points, % protection, | Jadad score = 3<br>No significant difference in HR<br>Author contacted. |
| Vilsvik, 1988 | RCT, (Latin square) double-blind, crossover. 2 control, 4 study days at same time in AM on different days (1-7 days apart). 9 excluded because did not show a | Norway. Recruitment: not described. N=12. 9 m, 3, f. Age: 20-45 (mean 29) Inclusion: asthma, reproducible EIB ( fall FEV1 at least 20% in 2 control tests 1 wk apart), FEV1 > 70% predicted, < | Randomised to: NCS 1 mg, 4 mg, 8 mg or placebo via identical MDI's 60 min pre exercise. Plasma concentrations monitored. | Used: Measured: PEFR pre/post tx, pre exercise, then 2, 5, 10, 15, and 30 min post exercise. Calculated: Maximum % fall PEFR, % protection, Side effects: 3 required | Jadad score = 4<br>No differences in HR.<br>SD calculated from individual patient data provided<br>Author contacted. |

| Study | Method | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| | reproducible fall of 20%. 2 excluded because > 15% variation from control day. Concomitant Tx: none on OHD or theophylline. Stopped IHD 8 h pre test. Exercise test: inclined treadmill, 6 min. t 22 C, RH 55%. HR monitored | 15% variability over study period. 9 of 23 subjects excluded because failed to demonstrate reproducible EIH, 2 of 23 showed > 15% variability. 12 subjects analysed. | | IHD rescue post placebo, 2 post NCS 1 mg. | |

Individual data provided.

**Table 4.1a** **Characteristics of included studies**

| Author | Country | Asthma | Atopy | Defn EIB | Mean max% fall Ctl run | sd | Tx dose | Delivery | Time of Pre-tx | N | Age range mean | adult | child | m | f | PFT reported |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Boner 1988 | Italy 4 days | yes | yes | 15% | 35.38 | 18.56 | 4 mg NCS | AA Spacer & MDI + spacer | 15 min | 13 | 7.5 - 13 10 | C | | 9 | 4 | FEV1 |
| Boner 1989 | Italy 2 days | yes | yes | 15% | 39.90 | 16.34 | 4 mg NCS | MDI | 30 min | 20 | 7.5 - 15 11.3 | C | | 15 | 5 | PEFR FEV1 FVC FEF |
| Bundgaard 1988 | Denmark 1 -2 wks | yes | ? | 20% | 37.43 | 15.11 | 2 mg NCS 4mg NCS | MDI | 30 min | 14 | 21 - 49 31 | A | | 6 | 8 | PEFR |
| Chudry 1987 duration | UK 2days in 1 wk | yes | ? | 20% | 40.60 | 15.50 | 4 mg NCS | MDI | 30, 150, 270 min | 12 | 8 - 15 yr | C | | 9 | 3 | FEV1 |
| Comis 1993 | Italy daily | yes | yes | 15% | 36.20 | 13.50 | 4 mg NCS 10 mg SCG | Spacer & MDI + spacer | 30 min | 12 | 8.5 - 13.5 | C | | 7 | 5 | FEV1 |
| De Benedictis 1994a | Italy sep days | yes | ? | 15% | 31.10 | 13.80 | 4 mg NCS 10 mg SCG | MDI | 20 min | 17 | 7 - 15 10.2 | C | | 11 | 6 | FEV1 |
| De Benedictis 1994b | Italy sep days | yes | ? | 15% | 38.80 | 11.20 | 4 mg NCS 10 mg SCG | MDI with spacer | 20 min | 8 | 7 - 11 8.7 | C | | 5 | 3 | FEV1 |
| De Benedictis 1995 duration | Italy sep days | yes | ? | 15% | 36.90 | 13.30 | 4 mg NCS 10 mg SCG | MDI | 20 min 140 min | 13 | 7 - 15 10 | C | | 9 | 4 | FEV1 |
| Debelic 1986 | Germany sep days | yes | yes | 20% | 50.42 | 14.70 | 4mg NCS | MDI | 30 min | 12 | 14 -19 16.9 | C | | 7 | 5 | FEV1 |
| Henriksen 1988 | Denmark ~1 wk | yes | yes | 20% | 50.00 | 16.63 | 4mg NCS | MDI | 30 min | 12 | 7 - 14 10.8 | C | | 10 | 2 | FEV1 PEFR |
| Konig 1987 duration | USA sep days | yes | ? | 20% | 36.40 | 11.90 | 4mg NCS 20 mg SCG | MDI | 20, 120, 240 min | 12 | 21 - 38 27.3 | A | | 12 | 0 | FEV1 PEFR |
| Morton 1992 | Australia sep days | yes | ? | 15% | 33.21 | 21.94 | 8mg NCS 4mg SCG | MDI | 15 min | 16 | 13-30 20 | A | | 10 | 6 | FEV1 |
| Novembre 1994s | Italy sep days | yes | yes | 15% | 28.70 | 13.30 | 4mg NCS | MDI with spacer | 20 min | 19 | 6 - 15 | C | | 13 | 6 | FEV1 PEFR FEF |
| Novembre 1994f | Italy sep days | yes | yes | 15% | 29.79 | 13.92 | 4 mg NCS 10 mg F | MDI with spacer | 20 min | 24 | 6 - 16 | C | | 16 | 8 | FEV1 PEFR FEF |
| Oseid 1995 | Norway sep days | yes | yes | 20% | 32.40 | 16.63 | 4mg NCS | MDI | 30 min | 20 | 15-28 18.9 | A | | 6 | 14 | FEV1 FVC FEF |
| Roberts 1985 | UK sep days | yes | yes | 20% | 40.60 | 16.50 | 2, 4mg NCS 4mg minocromil | MDI | 30 min | 9 | 16-49 | A | | 6 | 3 | FEV1 |
| Shaw 1985 | 1 wk part UK | yes | yes | 20% | 36.88 | 15.06 | 2mg NCS | MDI | 20 min | 8 | 17-47 | A | | 8 | 0 | FEV1 FVC |
| Todaro 1993 | Italy | yes | ? | 15% | 37.43 | 15.11 | 4mg NCS | MDI | 20 min | 13 | 19-31 25 | A | | 11 | 2 | FEV1 |
| Vilsvik 1988 | Norway sep days | yes | ? | 20% | | | 1mg, 4mg, 8mg NCS | MDI | 60 min | 12 | 20-45 29.0 | A | | 9 | 3 | PEFR |
| Mihalyka | Australia sep days | yes | ? | 20% | | | 4 mg NCS | MDI | 15 min | 14 | 15-45 | A | | | | PEFR |
| | | | | | mean 37.34 sd 5.84 | | | | | 280 | | Total | | 179 | 87 | |

## Appendix D

## Working document

## Jadad Validity Criteria

## Appendix D

## NCS use in EIB: Jadad's Validity Criteria

**CITATION #** **REVIEWER**

Please place a check mark beside your selection and provide a total score at the end.

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?
   YES = 1 point
   NO = 0 points

2. Was the study described as double-blind?
   YES = 1 point
   NO = 0 points

3. Was there a description of withdrawals and dropouts?
   YES = 1 point
   NO = 0 points

4. For question 1, the method to generate the sequence of randomization was described, and it was appropriate (table of random numbers, computer generated, etc.)
   YES = 1 point
   NO = 0 points

5. If for question 2, the method of double blinding was described, and it was appropriate (identical placebo, dummy etc.).

   YES = 1 point
   NO = 0 points

6. For question 1, the method to generate the sequence of randomization was described, and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number etc.)

   YES = -1 point

7. For question 2, the study was described as double blind but the method of blinding was inappropriate (e.g., the comparison of tablet vs. Injection with no double dummy).
8.
   YES = -1 point

**TOTAL** Jadad score _____

Concealment Allocation: Please place a check mark beside your selection

A = Adequate Concealment

B = Uncertain

C = Clearly Inadequate

## Appendix E

## Working document

## Letter to Author

October 24, 1997

Address

Dear Dr.

The Cochrane Collaboration (CC) is an international, multi-disciplinary, volunteer effort designed to produce high quality systematic reviews in many areas of health care. Using standardized approaches, the CC is attempting to produce, disseminate, and update these reviews to provide health care providers and patients with the "best evidence" for the treatment of medical illness. Within the CC, the Airways Review Group (ARG), with over 80 members from around the world, is working on systematic reviews that cover a wide range of topics in respiratory health care. Following rigorous peer review, each systematic review will be published in the Cochrane Library (CDSR) to which you may have access in your hospital library.

As members of the ARG, Dr. Duncan Saunders, Dr. Brian Rowe, and myself are in the process of conducting a systematic review on ***The attenuation of exercise-induced bronchoconstriction (EIB) using nedocromil sodium (NCS)***. We are specifically interested in all published and unpublished randomized, placebo-controlled clinical trials using inhaled NCS, a standardized exercise challenge, and objective pulmonary function test (pft) results from individuals with known, documented EIB.

We have selected one of your publications for possible inclusion:

Our research group is writing to you for several reasons. First, we wonder if you know of other trials of published or unpublished research performed by yourself or others that might deserve inclusion (a list of articles we have identified for possible inclusion is appended). Second, the CC methodology strongly encourages us to have the authors of the primary studies provide confirmation on the accuracy of data extracted from their article(s). As you can imagine, valid and reliable data extraction is necessary for an accurate "summary estimate" of the effect of treatment to be calculated. Third, we wonder if you would be able to provide further information on methodology and individual results at some time in the next two months? Your responses will be included in the "comments" section on the CDSR, and we will acknowledge your contribution in the publication.

Would you please complete the enclosed form and FAX it back to us at:
**403 492-0364** as soon as it is convenient. If you have access to e-mail you may also choose that mode of response. Our e-mail is: **carol@hippocrates.family.med.ualberta.ca.**

Thank you for your attention to this matter. We look forward to hearing from you.

Yours sincerely,

Carol Spooner, RN, BScN
Graduate Studies
Public Health Sciences

**ATTENUATION OF EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) USING NEDOCROMIL SODIUM (NSC)**
**~ A META-ANALYSIS ~**

Name: Dr.

1. Are you aware of any studies in addition to the appended list that relate to the above topic? (They may be published or unpublished, conducted by yourself or others, written in any language.)

   ❑ Yes ❑ No

   If yes, please list:

   1. _____
      _____
   2. _____
      _____

2. Would you be able to provide confirmation with respect to data extracted from your article? (We will mail or fax the data to you and ask that you check it for correctness and accuracy)

   ❑ Yes. Please provide your fax number _____

   ❑ No, however, _____ would be able to provide this service. He/she may be contacted at the following address, email or fax number:

_____
_____
_____

   ❑ No, I would not be able to do this.

3. At a later date, would it be possible for you to provide us with:
   a) Some additional basic results for an individual patient data analysis (such as: age, gender, placebo pft, NCS pft, etc. on each patient included in your publication):
      ❑ Yes ❑ No

   b) The treatment sequencing prior to the exercise challenge (i.e. whether treatment order was placebo-NCS or NCS -placebo) for each period of the crossover.
      ❑ Yes ❑ No

4. Could you please explain what method of randomization was used in this trial
   _____

Thank you for your cooperation.

**Please fax to**: ...

Studies for potential inclusion in meta-analysis of NCS in EIB


1. Albazzaz MK, Neale MG, Patel KR. Dose-response study of nebulised nedocromil sodium in exercise induced asthma. Thorax 1989; 44: 816-819

2. Albazzaz MK, Neale MG, Patel KR. Dose duration of nebulized nedocromil sodium in exercise-induced asthma. European Respiratory Journal 1992; 8:967-9

3. Bauer CP, Emmrich P. [Effect of nedocromil sodium on the hyperreactivity of the bronchial system in young asthmatic patients] [German] Monatsschrift Kinderheilkunde 1988;

4. Bauer CP. The protective effect of nedocromil sodium in exercise-induced asthma. European Journal of Respiratory Diseases 1986; 69:Suppl.147:252-254

5. Bleeker ER, Walden SM, Britt EJ. Effect of Nedocromil on exercise induced asthma. Journal of Allergy and Clinical Immunology 1985; 75:173 (abstract)

6. Boner AL, Miglioranzi P, Piacentini GL, Peroni DG, Bonetti S, Andreoli A. Effects of nedocromil sodium pressurized aerosol on exercise challenge using a spacer device and the normal adapter. Pediatric Asthma, Allergy and Immunology 1988; 2:207-213

7. Boner AL, Vallone G, Bennati D. Nedocromil sodium in exercise-induced bronchoconstriction in children. Annals of Allergy 1989; 62:38-41

8. Bundgaard A, Enehjelm SD, Schmidt A. A comparative study of the effects of two different doses of nedocromil sodium and placebo given by pressurized aerosol in exercise-induced bronchoconstriction. Allergy: European Journal of Allergy and Clinical Immunology 1988;

9. Cavallo A, Cassaniti C, Glogger A, Magrini H. Action of nedocromil sodium in exercise-induced asthma in adolescents. Journal of Investigational Allergology and Clinical Immunology 1995; 5:286-288

10. Chudry N, Correa F, Silverman M. Nedocromil sodium and exercise induced asthma. Archives of Disease in Childhood 1987; 62:412-4

11. Comis A, Valletta EA, Sette L, Andreoli A, Boner AL. Comparison of nedocromil sodium and sodium cromoglycate administered by pressurized aerosol, with and without a spacer device in exercise- induced asthma in children. European Respiratory Journal 1993; 6:

12. De Benedictis FM, Tuteri G, Bertotto A, Bruni L, Vaccaro R. Comparison of the protective effects of cromolyn sodium and nedocromil sodium in the treatment of exercise-induced asthma in children. Journal of Allergy and Clinical Immunology 1994; 94:684-688

13. De Benedictis FM, Tuteri G, Pazzelli P, Bertotto A, Bruni L, Vaccaro R. Cromolyn versus nedocromil: Duration of action in exercise-induced asthma in children. Journal of Allergy and Clinical Immunology. 1995; 96:510-514

14. De Benedictis FM, Tuteri G, Niccoli A, Mezzetti D, Rossi L, Bruni L. The effect of cromolyn sodium and nedocromil sodium administered by a pressurized aerosol with a spacer device on exercise-induced asthma in children. Mediators of Inflammation 1994; 3:S1:S35-S37

15. Debelic M. Nedocromil sodium and exercise-induced asthma in adolescents. European Journal of Respiratory Diseases 1986; 69:Suppl.147:266-267

16. Henriksen JM. Effect of nedocromil sodium on exercise-induced bronchoconstriction in children. Allergy 1988; 43:449-53

17. Hoffmeister BC, Casanova ZD. Sodium nedocromil and sodium cromoglycate in the prevention of exercise induced asthma. Revista Chilena de Pediatria 1995; 66:296-299

18. Konig P, Hordvik NL, Kreutz C. The preventive effect and duration of action of nedocromil sodium and cromolyn sodium on exercise-induced asthma (EIA) in adults. Journal of Allergy and Clinical Immunology 1987; 79:64-68

19. Magnussen H. The protective effect of Disodium cromoglycate (DSCG) and Nedocromil sodium on exercise-induced bronchial asthma. Atemwegs- und Lungenkrankheiten 1986; 12:9 S: S107-S109 GERMAN

20. Mihalyka MS, Anderson SD, Corte P. Nedocromil sodium in exercise induced asthma. Aust. & NZ J of Med 1987; 17(4 Suppl2):524 (abstract)

21. Morton AR, Ogle SL, Fitch KD. Effects of nedocromil sodium, cromolyn sodium, and a placebo in exercise-induced asthma. Annals of Allergy. 1992; 68:143-8

22. Novembre E, Frongia GF, Veneruso G, Vierucci A. Inhibition of exercise-induced-asthma (EIA) by nedocromil sodium and sodium cromoglycate in children. Pediatric Allergy and Immunology 1994; 5:107-110

23. Novembre E, Frongia G, Lombardi E, Veneruso G, Vierucci A. The preventive effect of nedocromil or furosemide alone or in combination on exercise-induced asthma in children. Journal of Allergy and Clinical Immunology 1994; 94:201-206

24. Oseid S, Mellbye E, Hem E. Effect of nedocromil sodium on exercise-induced bronchoconstriction exacerbated by inhalation of cold air. Scandinavian Journal of Medicine & Science in Sports 1995; 5:88-93

25. Patel KR, Albazzaz MK. Protective effect of cromolyn sodium and nedocromil sodium in exercise-induced asthma. J of Allergy and Clinical Immunology 1987; 79:187 (abstract)

26. Roberts JA, Thomson NC. Attenuation of exercise-induced asthma by pretreatment with nedocromil sodium and minocromil. Clinical Allergy 1985; 15:377-81

27. Shaw RJ, Kay AB. Nedocromil, a mucosal and connective tissue mast cell stabilizer, inhibits exercise-induced asthma. British Journal of Diseases of the Chest 1985; 79:385-9

28. Sinclair D G, Winfield CR. Attenuation of exercise induced asthma by nedocromil sodium and sodium cromoglycate. Journal of the Royal Army Medical Corps 1990; 136:105-6

29. Speelberg B, Verhoeff NPLG, Van den Berg NJ, Oosthoek CHA, Van Herwaarden CLA, Bruijnzeel PLB Nedocromil sodium inhibits the early and late asthmatic response to exercise. European Respiratory Journal 1992; 5:430-437

30. Thomson NC, Roberts JA. Nedocromil sodium attenuates exercise-induced asthma. European Journal of Respiratory Diseases 1986; 69, Suppl.147:297-298

31. Todaro A, Faina M, Alippi B, Dal Monte A, Ruggieri F. Nedocromil sodium in the prevention of exercise-induced bronchospasm in athletes with asthma. Journal of Sports Medicine and Physical Fitness 1993; 33:137-145

32. Vilsvik J, Schaanning J. A comparative study of the effect of three doses of nedocromil sodium and placebo given by pressurized aerosol to asthmatics with exercise-induced bronchoconstriction. Annals of Allergy 1988; 61:367-70

## Appendix F

## Working document

## Data extraction form for individual primary study author

## ATTENUATION OF EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) USING NEDOCROMIL SODIUM (NSC)
## ~ A META-ANALYSIS ~

TRIAL 1994b: de Benedictis FM, Tuteri G, Niccoli A, Mezzetti D, Rossi L, Bruni L. The effect of cromolyn sodium and nedocromil sodium administered by a pressurized aerosol with a spacer device on exercise-induced asthma in children. Mediators of Inflammation 1994; 3:S1:S35-S37

In the above trial:
Which method of randomization was used? _____

How was blinding of the treatments achieved? _____

We have extracted the following data from the publication identified above.
1. Could you confirm or correct the numbers provided in the table.
2. Could you please fill in the blanks where it is possible for you to do so.

| Subject | Age | Sex M or F | Tx order: 1. pl-NCS-SCG 2. NCS-pl-SCG 3. pl-SCG-NCS 4. NCS-SCG-pl | Dates of challenges | Max. % fall control FEV1 | Max. % fall placebo FEV1 | Max. % fall NCS FEV1 | Max. % fall SCG FEV1 |
|---|---|---|---|---|---|---|---|---|
| 1 | | | | | 40.20 | 22.10 | 6.30 | 20.10 |
| 2 | | | | | 61.40 | 35.30 | 32.70 | 15.90 |
| 3 | | | | | 28.00 | 1.30 | 0.60 | 10.00 |
| 4 | | | | | 36.00 | 18.00 | 5.60 | 9.90 |
| 5 | | | | | 45.30 | 52.90 | 17.10 | 16.90 |
| 6 | | | | | 38.60 | 67.40 | 52.30 | 28.60 |
| 7 | | | | | 36.80 | 24.70 | 0.00 | 0.00 |
| 8 | | | | | 24.80 | 29.50 | 3.80 | 5.10 |
| Mean | | | | | 38.89 | 31.40 | 14.80 | 13.30 |
| SD | | | | | 11.21 | 20.68 | 18.63 | 8.90 |

Do you have any data on whether the participants liked NCS, would use it in preference to another drug, felt their performance improved, or other subjective comments? If so, could you pass along this information? It does not need to have been analyzed, we are just interested in having a look at the comments if they are available.

**ATTENUATION OF EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) USING NEDOCROMIL SODIUM (NSC)**
**~ A META-ANALYSIS ~**

TRIAL 1995: de Benedictis FM, Tuteri G, Pazzelli P, Bertotto A, Bruni L, Vaccaro R. Cromolyn versus nedocromil: Duration of action in exercise-induced asthma in children. Journal of Allergy and Clinical Immunology. 1995; 96:510-514

## 40 minute results

| Subject | Age | Sex M or F | Tx order: 1. pl-NCS-SCG 2. NCS-pl-SCG 3..pl-SCG-NCS 4. NCS-SCG-pl | Dates of challenges | Max. % fall control FEV1 | Max. % fall placebo FEV1 | Max. % fall NCS FEV1 | Max. % fall SCG FEV1 |
|---|---|---|---|---|---|---|---|---|
| 1 | | | | | 51.40 | 35.50 | 31.80 | 38.20 |
| 2 | | | | | 40.20 | 21.50 | 15.00 | 4.2 |
| 3 | | | | | 61.40 | 43.80 | 23.80 | 47.80 |
| 4 | | | | | 24.80 | 22.80 | 18.70 | 22.50 |
| 5 | | | | | 17.60 | 6.00 | 5.60 | 9.80 |
| 6 | | | | | 36.00 | 10.40 | 15.50 | 10.30 |
| 7 | | | | | 45.30 | 35.20 | 38.50 | 41.60 |
| 8 | | | | | 16.30 | 30.50 | 47.00 | 4.00 |
| 9 | | | | | 43.80 | 34.70 | 0.00 | 4.10 |
| 10 | | | | | 38.60 | 53.60 | 64.20 | 58.70 |
| 11 | | | | | 31.50 | 27.70 | 13.30 | 13.10 |
| 12 | | | | | 22.70 | 15.90 | 37.90 | 24.70 |
| 13 | | | | | 36.80 | 23.50 | 0.00 | 6.20 |
| Mean | | | | | 36.9 | 25.5 | 23.9 | 21.90 |
| SD | | | | | 13.3 | 14.3 | 19.1 | 18.80 |

Thank you very much for your cooperation.

## ATTENUATION OF EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) USING NEDOCROMIL SODIUM (NSC)

### ~ A META-ANALYSIS ~

de Benedictis FM, Tuteri G, Bertotto A, Bruni L, Vaccaro R. Comparison of the protective effects of cromolyn sodium and nedocromil sodium in the treatment of exercise-induced asthma in children. Journal of Allergy and Clinical Immunology 1994; 94:684-688

In the above trial:
Which method of randomization was used? _____
How was blinding of the treatments achieved? _____

We have extracted the following data from the publication identified above.
1. Could you confirm or correct the numbers provided in the table.
2. Could you please fill in the blanks where it is possible for you to do so.

| Subject | Age | Sex M or F | Tx order: 1. pl-NCS-SCG 2. NCS-pl-SCG 3. pl-SCG-NCS 4. NCS-SCG-pl | Dates of challenges | Max. % fall control FEV1 | Max. % fall placebo FEV1 | Max. % fall NCS FEV1 | Max. % fall SCG FEV1 |
|---|---|---|---|---|---|---|---|---|
| 1 | | | | | 51.40 | 53.50 | 36.50 | 38.00 |
| 2 | | | | | 26.40 | 20.60 | 1.70 | 7.90 |
| 3 | | | | | 40.20 | 22.10 | 20.10 | 6.30 |
| 4 | | | | | 61.40 | 35.30 | 16.70 | 33.00 |
| 5 | | | | | 28.00 | 1.30 | 10.90 | 0.60 |
| 6 | | | | | 36.00 | 18.50 | 10.10 | 5.60 |
| 7 | | | | | 45.30 | 52.90 | 16.70 | 18.00 |
| 8 | | | | | 16.30 | 19.60 | 36.60 | 3.50 |
| 9 | | | | | 43.80 | 34.60 | 9.20 | 5.40 |
| 10 | | | | | 38.60 | 67.40 | 29.40 | 54.10 |
| 11 | | | | | 20.40 | 16.90 | 8.80 | 10.70 |
| 12 | | | | | 22.70 | 23.40 | 5.20 | 17.30 |
| 13 | | | | | 17.60 | 9.30 | 8.40 | 11.80 |
| 14 | | | | | 16.60 | 33.30 | 9.00 | 2.70 |
| 15 | | | | | 17.90 | 10.90 | 0.00 | 3.40 |
| 16 | | | | | 18.30 | 26.10 | 20.10 | 11.60 |
| 17 | | | | | 27.40 | 19.60 | 5.50 | 8.00 |
| Mean | | | | | 31.08 | 27.37 | 14.41 | 14.4 |
| SD | | | | | 13.78 | 17.26 | 11.09 | 11.1 |

# Appendix G

## Meta View graphs for sub-group analysis


Figure 4.7 Age: FEV1

Figure 4.8 Age: PEFR

Figure 4.9 Dose: FEV1

Figure 4.10 Dose: PEFR

Figure 4.11 Delivery system: FEV1

Figure 4.12 Delivery system: PEFR

Figure 4.13 Time of delivery: FEV1

Figure 4.14 Time of delivery: PEFR

Figure 4.15 Severity: FEV1

Figure 4.16 Severity: PEFR

Figure 4.17 Maximum % fall FVC

Figure 4.18 Maximum % fall FEF25-75

Figure 4.20 Duration of effect: FEV1

Figure 4.21 Sensitivity analysis, Jadad score: FEV1

Figure 4.22 Sensitivity analysis, Jadad score: PEFR

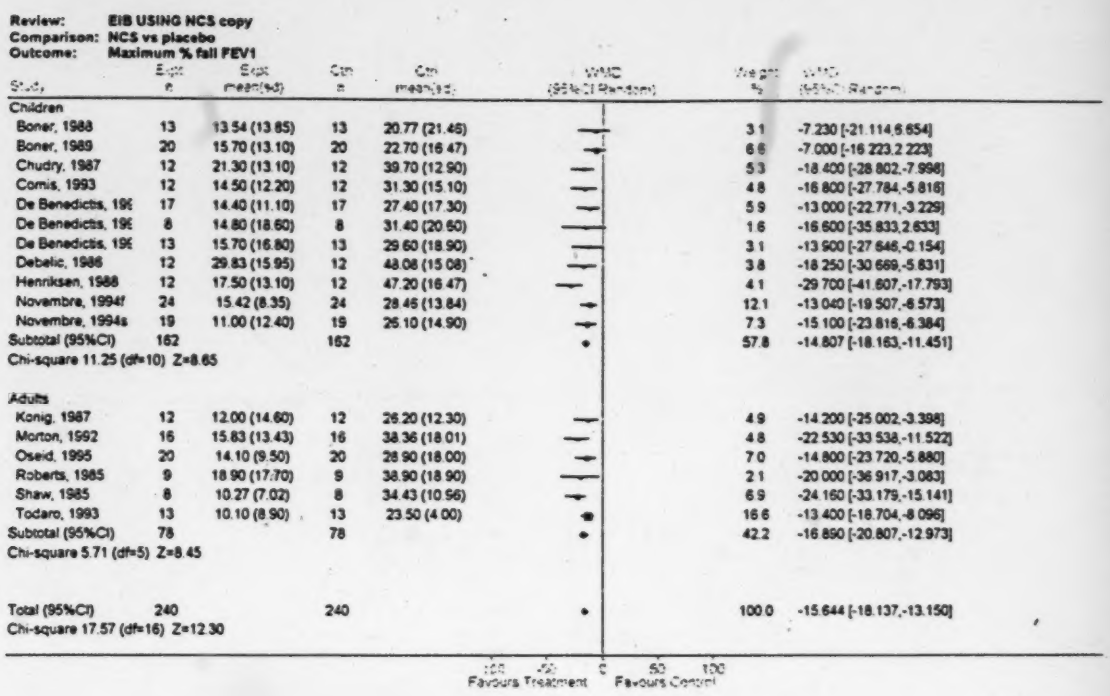



**Figure 4.7 Sub-grouped by Age: FEV1**

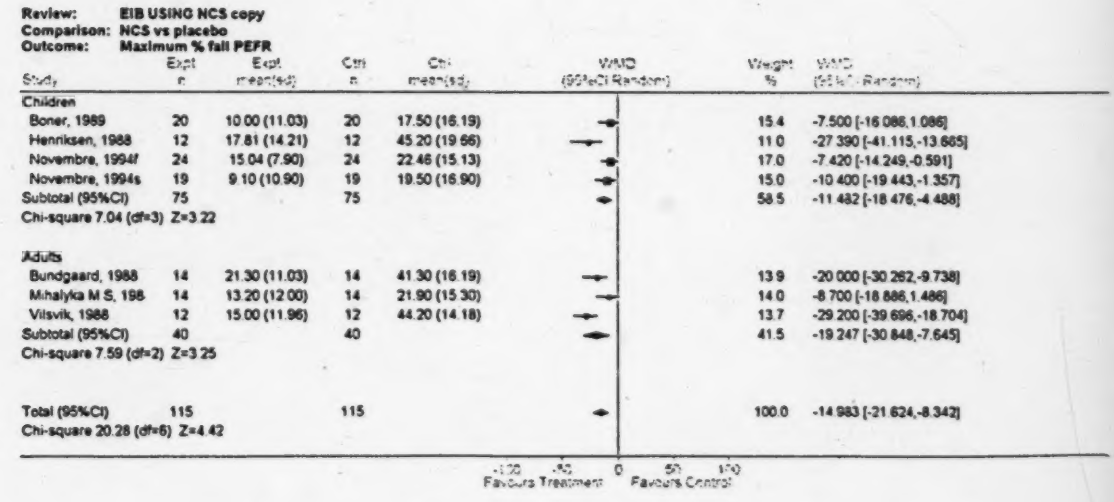



**Figure 4.8 Sub-group by Age: PEFR**

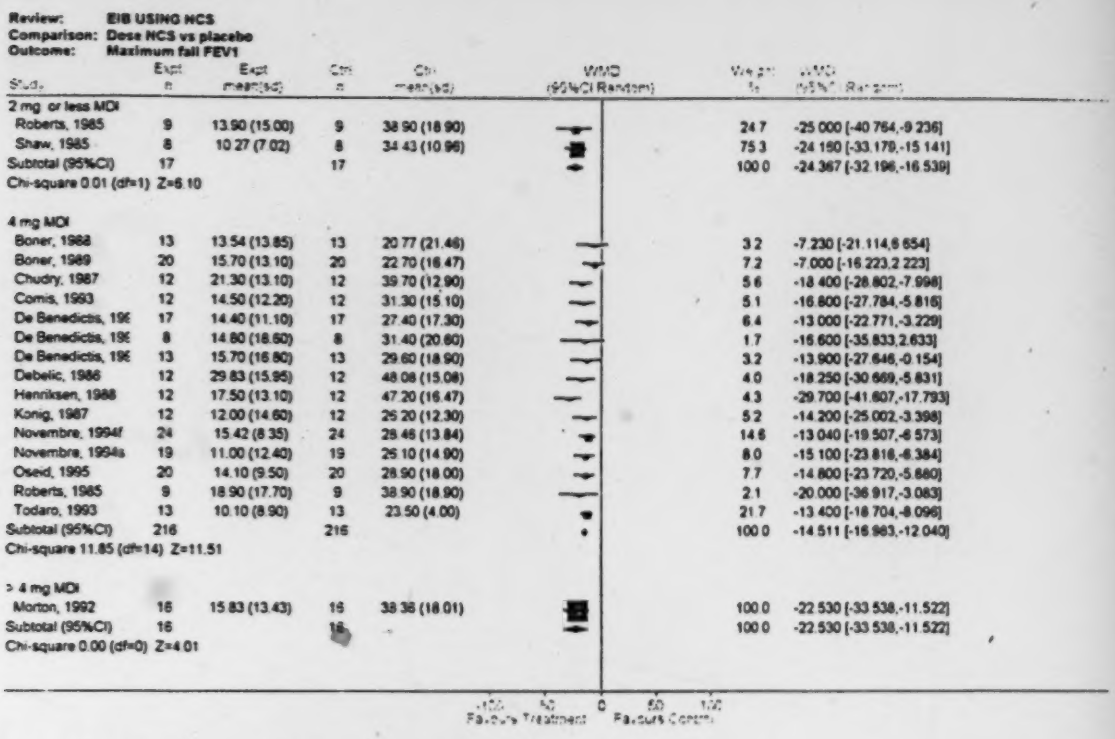



**Figure 4.9 Sub-grouped by Dose: FEV1**

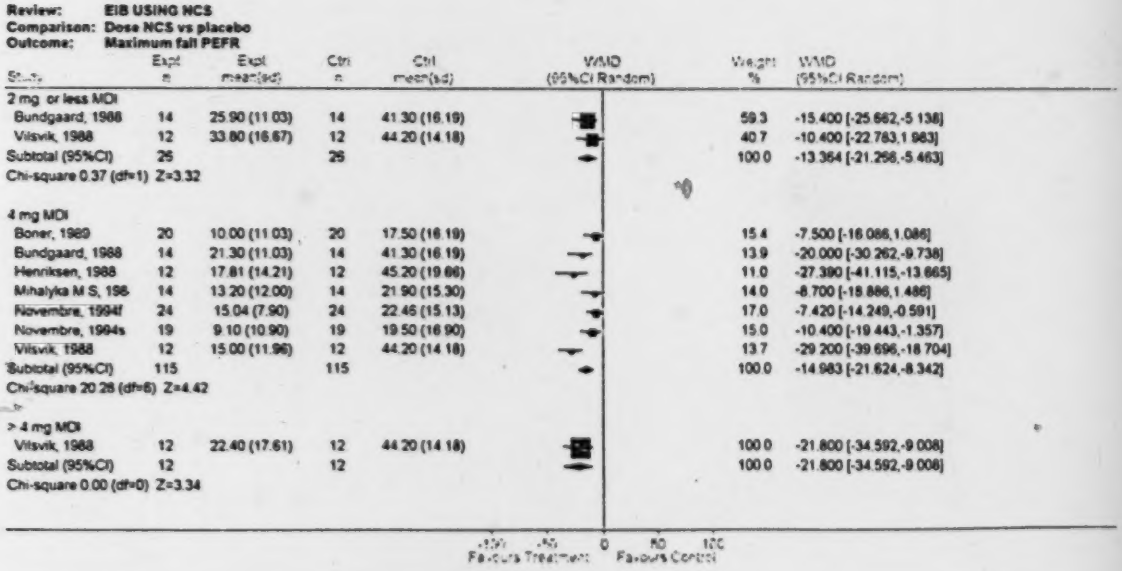



**Figure 4.10 Sub-group by Dose: PEFR**

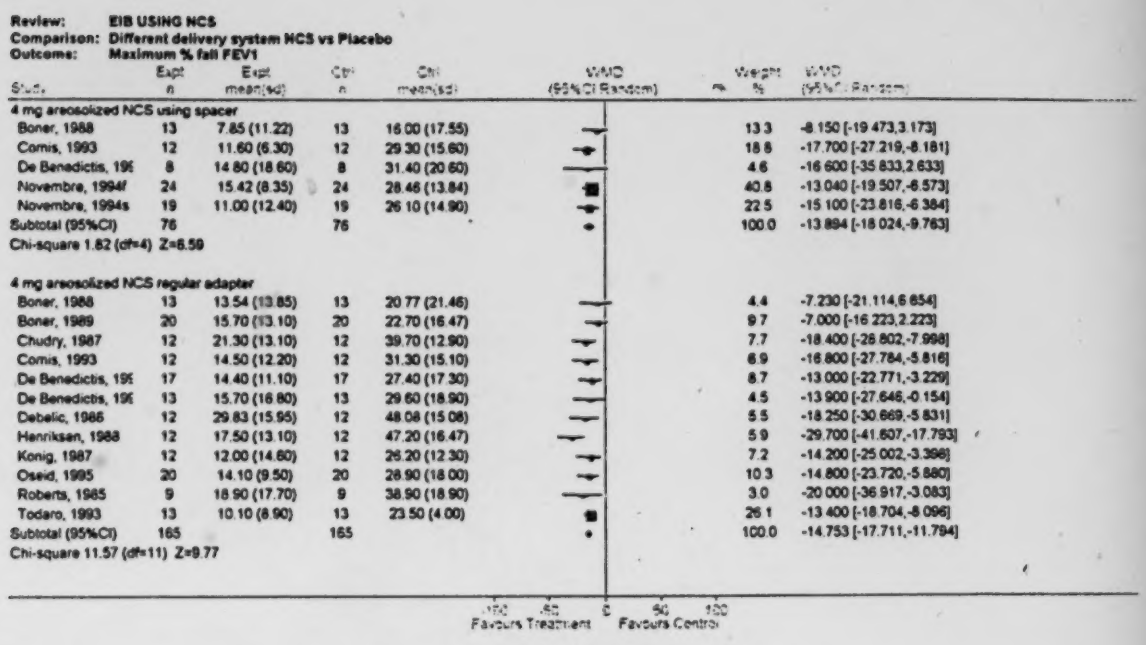



**Figure 4.11 Sub-grouped by Delivery system: FEV1**

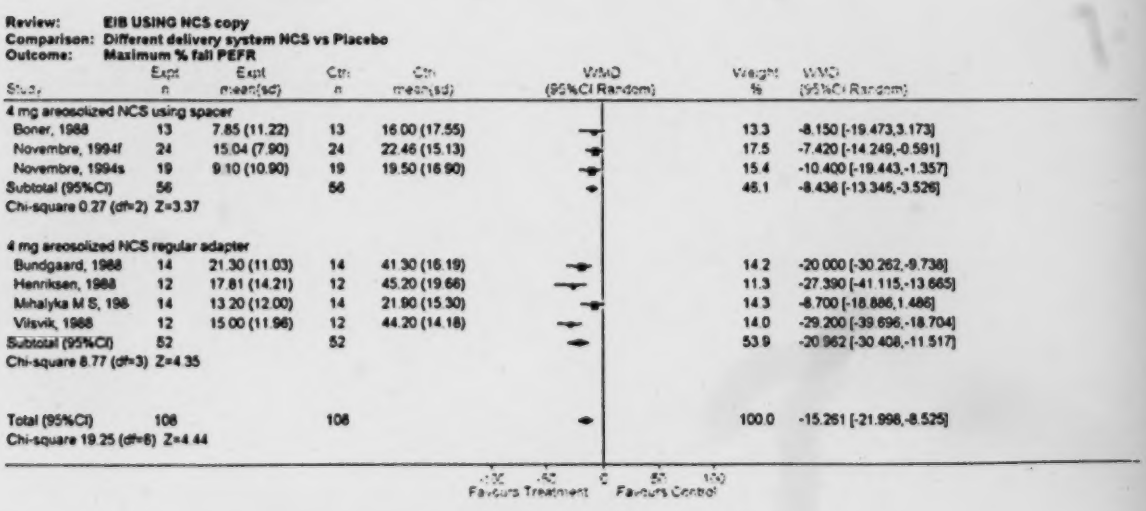



**Figure 4.12 Sub-group by Delivery system: PEFR**

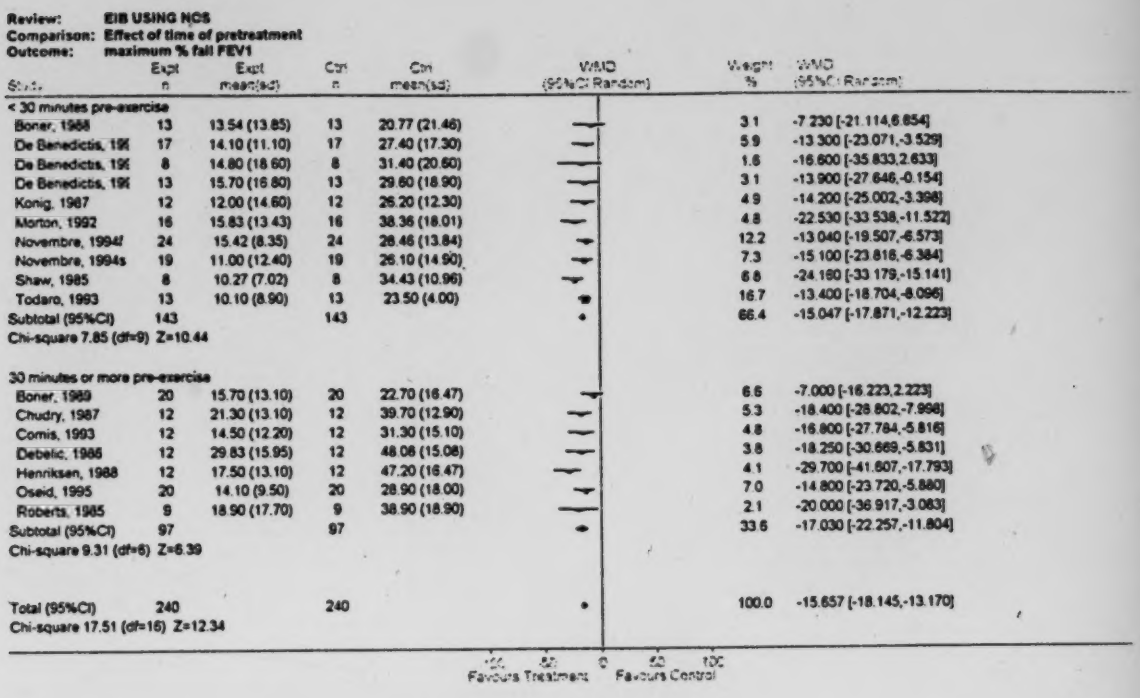



**Figure 4.13 Sub-grouped by time of pre-delivery: FEV1**

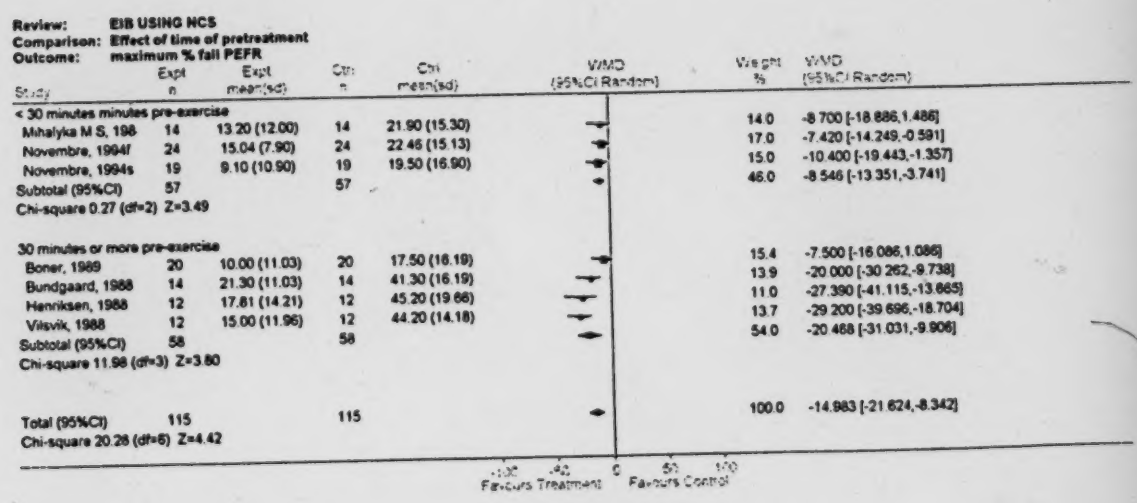



**Figure 4.14 Sub-group by time of pre-delivery: PEFR**

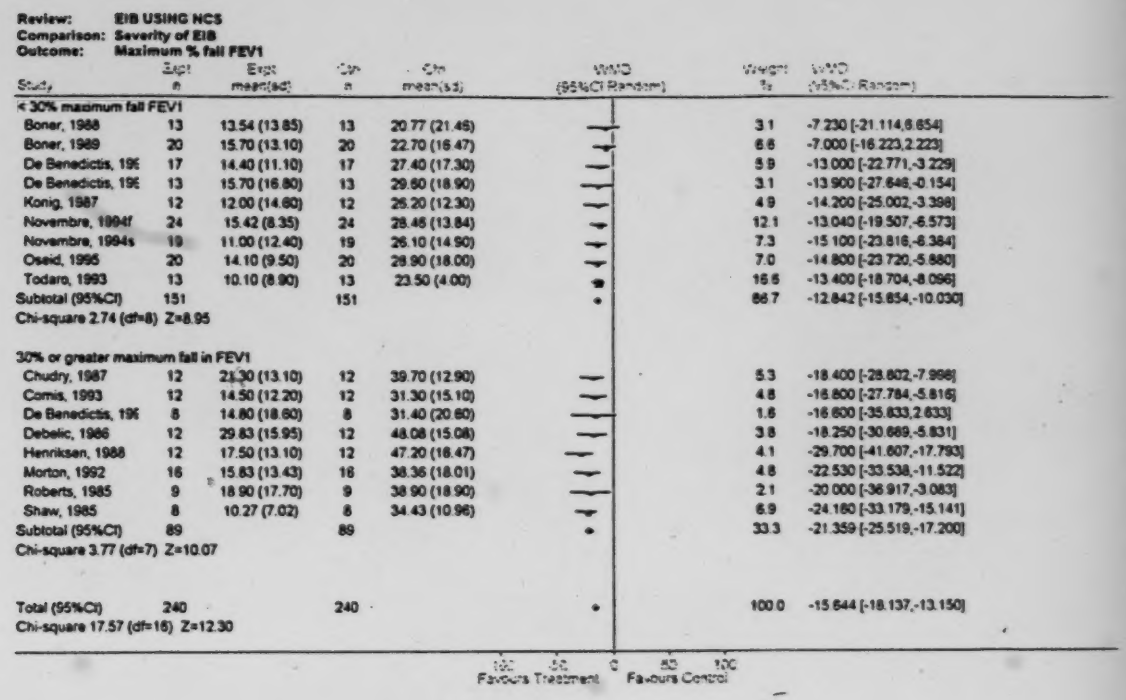



**Figure 4.15 Sub-grouped by severity: FEV1**

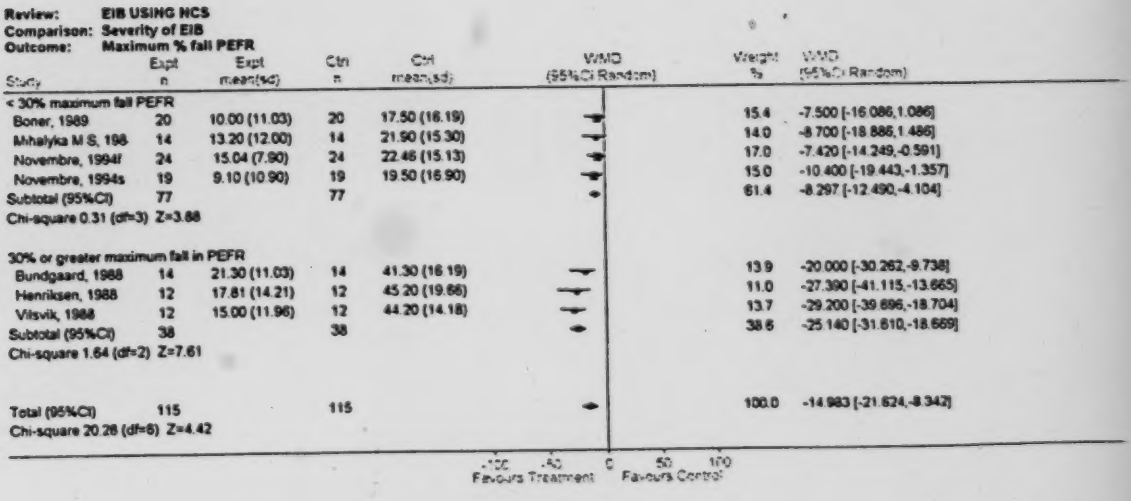
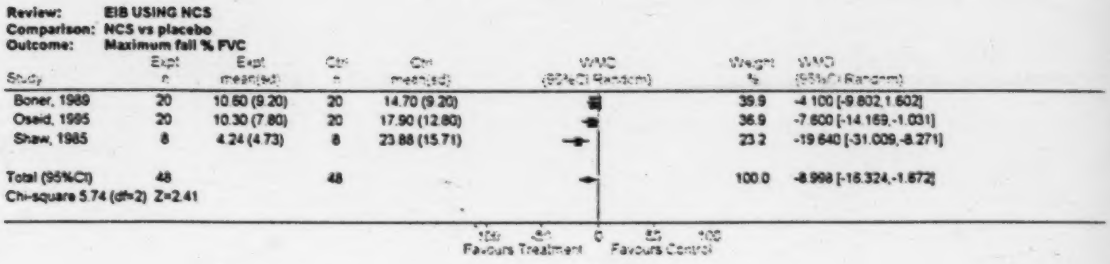
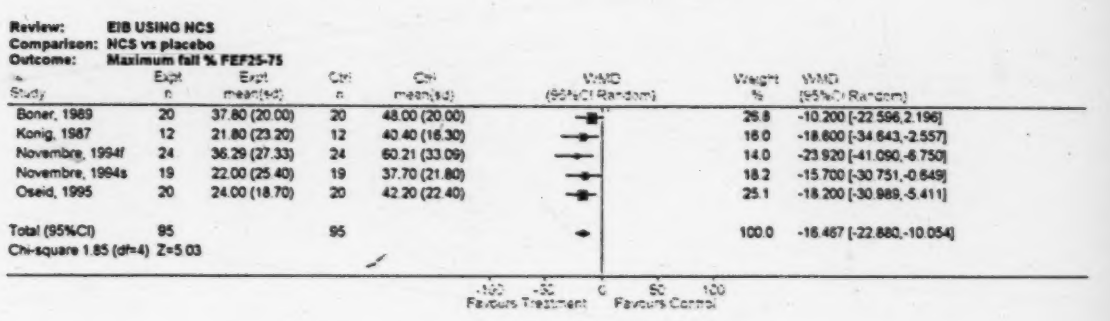


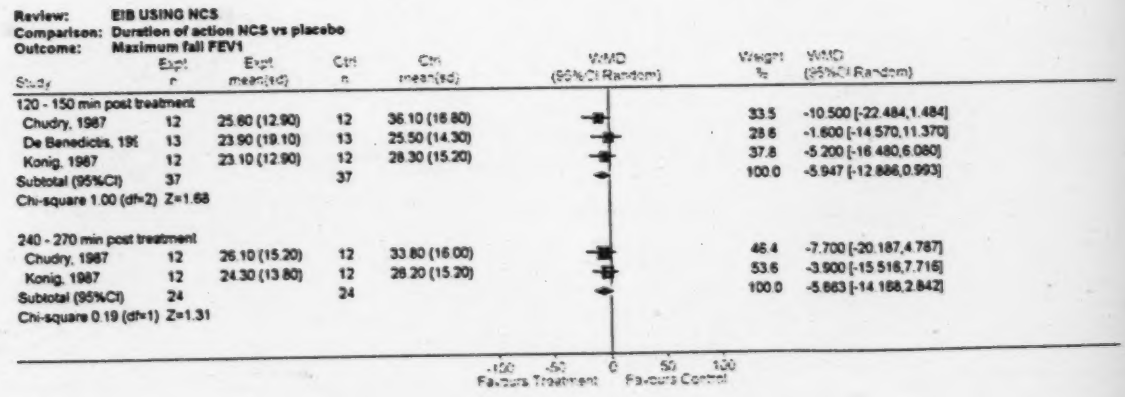

**Figure 4.16 Sub-group by severity: PEFR**


Review: EIB USING NCS
Comparison: NCS vs placebo
Outcome: Maximum fall % FVC
Study | Expt n | Expt mean(sd) | Ctrl n | Ctrl mean(sd) | WMD (92%CI Random) | Weight % | WMD (95%CI Random)
Boner, 1989 | 20 | 10.60 (9.20) | 20 | 14.70 (9.20) | 39.9 | -4.100 [-9.802,1.602]
Oseid, 1995 | 20 | 10.30 (7.80) | 20 | 17.90 (12.80) | 36.9 | -7.600 [-14.169,-1.031]
Shaw, 1985 | 8 | 4.24 (4.73) | 8 | 23.88 (15.71) | 23.2 | -19.640 [-31.009,-8.271]
Total (95%CI) | 48 | | 48 | | 100.0 | -8.998 [-16.324,-1.672]
Chi-square 5.74 (df=2) Z=2.41
-100 -50 0 50 100
Favours Treatment
Favours Control

## Figure 4.17 Maximum % fall FVC




## Figure 4.18 Maximum % fall FEF25-75




## Figure 4.20 Duration of effect: FEV1

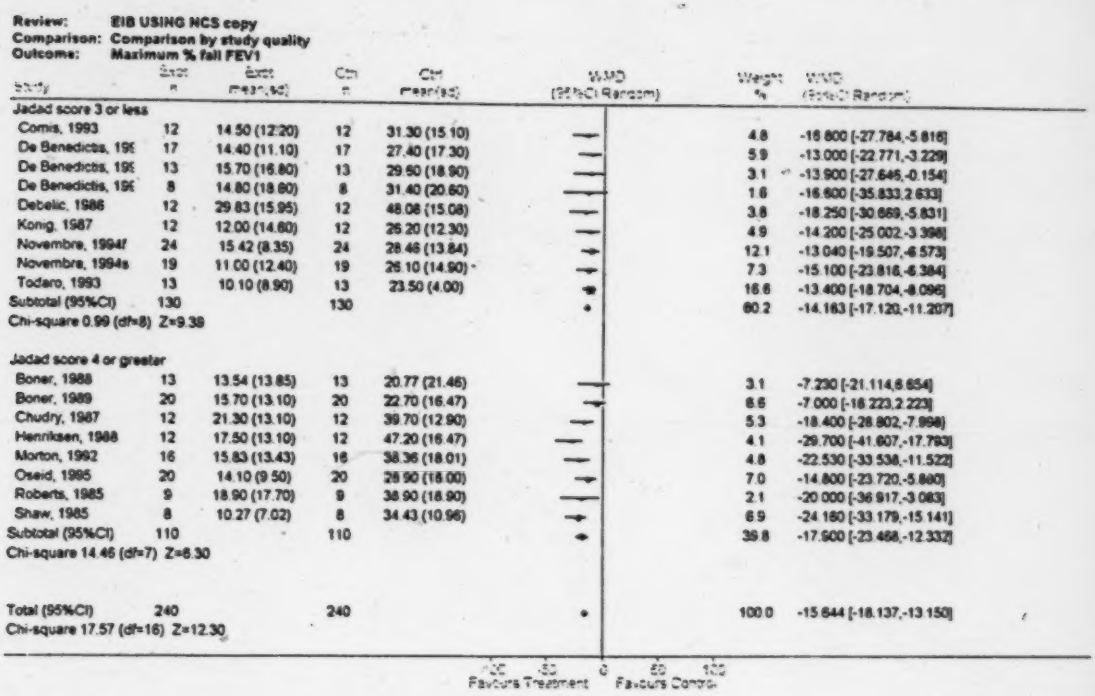



**Figure 4.21 Sensitivity analysis, Jadad score: FEV1**

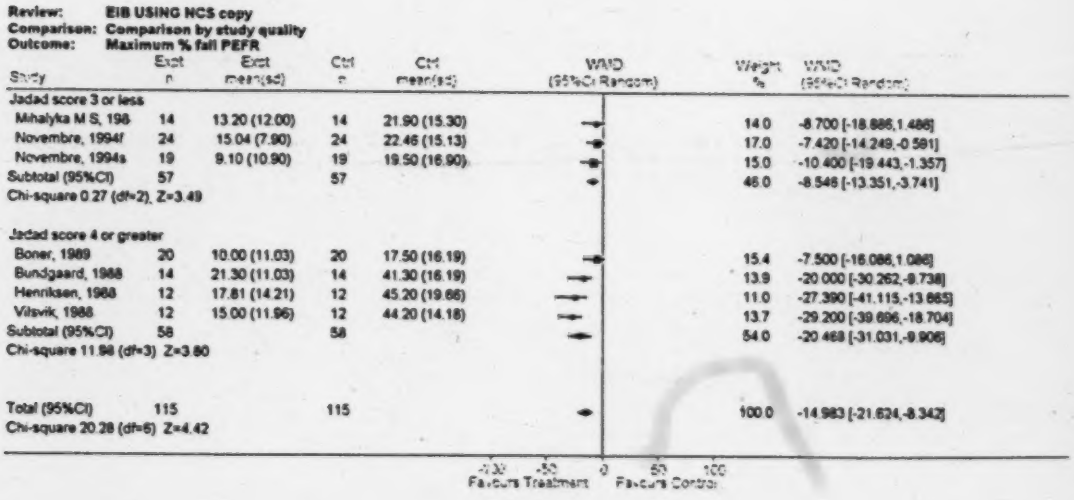



**Figure 4.22 Sensitivity analysis, Jadad score: PEFR**